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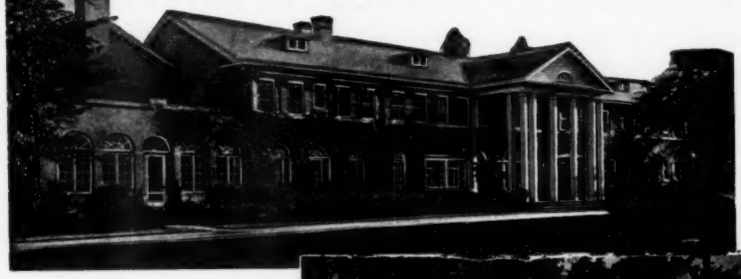

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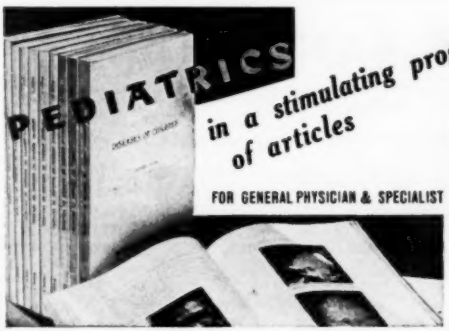

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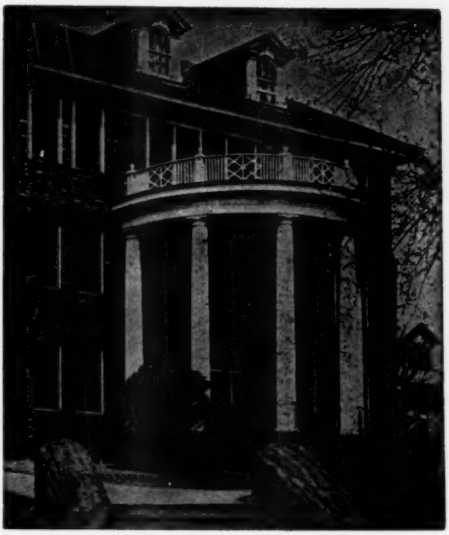

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A. M. A.
Archives of Neurology and Psychiatry

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STANDING POTENTIAL CORRELATES OF HYPNOSIS AND NARCOSIS

LEONARD J. RAVITZ, M.D.*
NEW HAVEN, CONN.

ALTHOUGH more than 150 years have elapsed since Galvani first associated electricity with living systems, accurate determination of electrical phenomena did not occur until relatively recent times. With the advent of electrocardiography and electroencephalography, A.C. potentials could be successfully detected; D.C. determinations, however, were beset with numerous difficulties, transcended only in the past few years.

To validate the concept that living organisms consist of electrical fields, Burr, with the assistance of Lane and Nims,[1] perfected a microvoltmeter by means of which basic electrical properties of living systems can be measured. Experiments of the past 16 years have clearly demonstrated that in vertebrates, invertebrates[2] and plants[3] there is a relatively steady, stable voltage gradient of considerable magnitude between any two points—altered only by changes in the fundamental biology of the organism—which exists in well defined patterns characteristic of the species and to some extent characteristic of the individual.[4] Voltage gradients between head and tail of chick embryos[5] and Amblystoma[6] can be determined even when the electrodes are 2 mm. from the surface. The sciatic nerve of the frog when stimulated produces an electrical field in the surrounding air detectable at a distance of 6 mm.[7] Potential differences have been recorded throughout

From the Section of Neuro-Anatomy, Yale University School of Medicine, New Haven, Conn.

*Now at the Department of Neuropsychiatry, Duke University School of Medicine, Durham, N. C.

1. (*a*) Burr, H. S.; Lane, C. T., and Nims, L. F.: A Vacuum Tube Microvoltmeter for the Measurement of Bio-Electric Phenomena, Yale J. Biol. & Med. **9**:65-76, 1936. (*b*) Burr, H. S., and Mauro, A.: Millivoltmeters, ibid. **21**:249-253, 1949.

2. Burr, H. S., and Hammett, F. F.: A Preliminary Study of Electrical Correlates of Growth in Obelia Geniculata, Growth **3**:211-220, 1939.

3. Burr, H. S.: An Electrometric Study of Mimosa, Yale J. Biol. & Med. **15**:823-829, 1943.

4. (*a*) Burr, H. S.: Potential Gradients in Living Systems and Their Measurements, M. Physics, vol. I, pp. 1117-1121, 1944; (*b*) vol. II, pp. 90-94, 1950. (*c*) Burr, H. S., and Northrop, F. S. C.: Evidence for the Existence of an Electro-Dynamic Field in Living Organisms, Proc. Nat. Acad. Sc. **25**:284-288, 1939.

5. Burr, H. S., and Hovland, C. I.: Bio-Electric Potential Gradients in the Chick, Yale J. Biol. & Med. **9**:247-258, 1937.

6. Burr, H. S., and Hovland, C. I.: Bio-Electric Correlates of Development in Amblystoma, Yale J. Biol. & Med. **9**:541-549, 1937.

7. Burr, H. S., and Mauro, A.: Electrostatic Fields of the Sciatic Nerve in the Frog, Yale J. Biol. & Med. **21**:455-462, 1949.

different stages of early development in Amblystoma.[8] It has been shown that a salamander embryo or free-swimming larva revolving between tips of capillary electrodes as a result of ciliary action causes galvanometer oscillations, the embryo or larva acting as an A.C. generator of very low frequency. A copper rod with solder on one end causes similar alternating phenomena, in contrast to a rotating glass rod, which produces no electrical effects.[4e] In the frog, the existence of an electrical pattern in unfertilized eggs which predicts the longitudinal axis of the developing nervous system has been unequivocally shown,[9] as have significant relationships between electrical patterns of young fruits and the ultimate shape of the gourds.[10] It is possible to predict the subsequent growth history of individual corn [11] and cotton [12] seeds from their mean potential differences. Wound healing in man has electrical correlates similar to those found in other species and of the same nature as are found in growth [13]; D.C. correlates of pattern vision have been studied [14]; cyclic variations in trees,[15] men,[16] and mice,[15d] unrelated to changes in the immediate environment, have been electrically recorded; ovulation time can be determined even from finger tip potentials,[17] and recent studies indicate that a malignant growth in the female genitourinary tract is detectable by this procedure,[18] which in mice [19] can differentiate neoplastic from embryonic tissue.[20]

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8. Burr, H. S., and Bullock, T. H.: Steady-State Potential Differences in the Early Development of Amblystoma, Yale J. Biol. & Med. **14**:51-57, 1941.

9. Burr, H. S.: Field Properties of the Developing Frog's Egg, Proc. Nat. Acad. Sc. **27**:276-281, 1941.

10. Burr, H. S., and Sinnott, E. W.: Electrical Correlates of Form in Cucurbit Fruits, Am. J. Botany **31**:249-253, 1944.

11. Burr, H. S.: Electrical Correlates of Growth in Corn Roots, Yale J. Biol. & Med. **14**:581-588, 1942; Electrical Correlates of Pure and Hybrid Strains of Sweet Corn, Proc. Nat. Acad. Sc. **29**:163-166, 1943. Nelson, O. E., Jr., and Burr, H. S.: Growth Correlates of Electromotive Forces in Maize Seeds, Proc. Nat. Acad. Sc. **32**:73-84, 1946.

12. Burr, H. S.: An Electrometric Study of Cotton Seeds, J. Exper. Zool. **113**:201-210, 1950.

13. Burr and Hammett.[2] Burr, H. S.; Harvey, S. C., and Taffel, M.: Bio-Electric Correlates of Wound Healing, Yale J. Biol. & Med. **11**:104-107, 1938. Burr, H. S.; Taffel, M., and Harvey, S. C.: An Electrometric Study of the Healing Wound in Man, ibid. **12**:483-485, 1940.

14. Köhler, W., and Held, R.: The Cortical Correlate of Pattern Vision, Science **110**: 414-419, 1949.

15. Burr, H. S.: (*a*) Moon-Madness, Yale J. Biol. & Med. **16**:249-256, 1944; (*b*) Diurnal Potentials in the Maple Tree, ibid. **17**:727-734, 1945; (*c*) Tree Potentials, ibid. **19**:311-318, 1947; (*d*) Electro-Cyclic Phenomena: Recording Life Dynamics of Oak Trees, Yale Scient. Mag. **25**:9-10, 32, 34, 36, 38, 40, 1950.

16. Ravitz, L. J.: Daily Variations of Standing Potential Differences in Humans, Yale J. Biol. & Med., to be published.

17. Burr, H. S.; Hill, R. T., and Allen, E.: Detection of Ovulation in the Intact Rabbit, Proc. Soc. Exper. Biol. & Med. **33**:109-111, 1935. Burr, H. S., and Musselman, L. K.: Bio-Electric Phenomena Associated with Menstruation, Yale J. Biol. & Med. **9**:155-158, 1936; Bio-Electric Correlates of the Menstrual Cycle in Women, Am. J. Obst. & Gynec. **35**:743-751, 1938. Burr, H. S.; Musselman, L. K.; Barton, D. S., and Kelly, N. B.: A Bio-Electric Record of Human Ovulation, Science **86**:312, 1937; Bio-Electric Correlates of Human Ovulation, Yale J. Biol. & Med. **10**:155-160, 1937. Langman, L., and Burr, H. S.: Electrometric Timing of Human Ovulation, Am. J. Obst. & Gynec. **44**:223-230, 1942.

18. Langman, L., and Burr, H. S.: (*a*) Electrometric Studies in Women with Malignancy of Cervix Uteri, Science **105**:209-210, 1947; (*b*) A Technique to Aid in the Detection of Malignancy of the Female Genital Tract, Am. J. Obst. & Gynec. **57**:274-281, 1949.

Lund's experiments furnish further evidence for the existence of electrical fields which when modified by external forces result in significant changes in biologic organization.[21] Thus, exploration of electrical phenomena has been carried out on a wide range of living membranes, tissues, cells and organisms—from bacteria [22] to man—and the results have been interpreted as valid evidence for the occurrence of quasielectrostatic fields [23] which seem to obey physical laws.[24]

The question arose as to whether this technique might shed light on the phenomenon of hypnosis, as it seemed inconceivable that the striking experimental and therapeutic results often achieved from such dissociated states do not affect in some way the fundamental biology of living organisms despite repeated failure to detect electrometric correlations with electroencephalographic alterations from trance states,[25] in contrast to electroencephalographic changes associated with injec-

19. Burr, H. S.: Biologic Organization and the Cancer Problem, Yale J. Biol. & Med. **12**:277-282, 1940; Changes in the Field Properties of Mice with Transplanted Tumors, ibid. **13**:783-788, 1941. Burr, H. S.; Smith, G. M., and Strong, L. C.: Bio-Electric Properties of Cancer-Resistant and Cancer-Susceptible Mice, Am. J. Cancer **32**:240-248, 1938; Electrometric Studies of Tumors Induced in Mice by the External Application of Benzpyrene, Yale J. Biol. & Med. **12**:711-717, 1940. Burr, H. S.; Strong, L. C., and Smith, G. M.: Bio-Electric Correlates of Methyl-Colanthrene-Induced Tumors in Mice, ibid. **10**:539-544, 1938.

20. Burr, H. S.: Electrometric Comparison of Neoplastic and Normal Growth: Unpublished data.

21. Lund, E. J.: Bioelectric Fields and Growth, Austin, University of Texas Press, 1947. A complete bibliography of bio-electric phenomena by H. F. Rosene appears in this book.

22. Burr, H. S., and Smith, G. H.: Unpublished data.

23. These change slowly with time (as contrasted with electrostatic fields). Burr and Mauro.[7]

24. (*a*) Burr, H. S.: An Electro-Dynamic Theory of Development Suggested by Studies of Proliferation Rates in the Brain of Amblystoma, J. Comp. Neurol. **56**:347-370, 1932; (*b*) Electricity and Life, Yale Scient. Mag. **18**:5-6, 16, 18, 1944; (*c*) Field Theory in Biology, Scient. Monthly **64**:217-225, 1947. (*d*) Burr, H. S., and Northrop, F. S. C.: The Electro-Dynamic Theory of Life, Quart. Rev. Biol. **10**:322-333, 1935; (*e*) footnote 4 c. (*f*) Northrop, F. S. C., and Burr, H. S.: Experimental Findings Concerning the Electro-Dynamic Theory of Life and an Analysis of Their Physical Meaning, Growth **1**:78-88, 1937.

25. Electroencephalographic alterations during hypnosis have been recorded during various suggestions, although these were apparently no different from those observed in the waking state (Barker, W., and Burgwin, S.: Brain Wave Patterns Accompanying Changes in Sleep and Wakefulness During Hypnosis, Psychosom. Med. **10**:317-326, 1948). However, Franke and Koopman (Franke, L. J., and Koopman, L. J.: Parallelismen in elektrobiologischen Vorgängen der Hirnrinde bei pathopsychologischen und parapsychologischen Erscheinungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:259-288, 1938) apparently recorded increased frequencies and voltages during trance conditions, which returned to normal in the posthypnotic state. In addition, they claimed that after a Fourier analysis the electroencephalographic curve was angular, i. e., the shape of a relaxation vibration, in contrast to the normal sinusoidal curve of the waking state. As these results have not been confirmed by others, their meaning cannot be assessed at this time (Dynes, J. B.: An Objective Method for Distinguishing Sleep from the Hypnotic Trance, Arch. Neurol. & Psychiat. **57**:84-93 [Jan.] 1947. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Brain Potentials During Hypnosis, Science **83**:239-241, 1936; Electrical Potentials of the Human Brain, J. Exper. Psychol. **19**:249-279, 1936. Lundholm, H., and Löwenbach, H.: Hypnosis and the Alpha Activity of the Electro-Encephalogram, Character & Personality **11**:145-149, 1942).

tion of barbiturates.[26] Because the electroencephalograms and the metabolic rates [27] differ during sleep and hypnosis, it has been postulated by some that such states are dissimilar, although other investigators have maintained that these phenomena are in some way related.[28] It is known that the tremor of paralysis agitans is usually abolished or diminished during sleep; yet this tremor can likewise be ameliorated in the trance condition.[29]

No completely objective criteria of hypnosis have yet been formulated; the depth of a trance is generally evaluated by empirical observation of the subject's ability to experience varying degrees of amnesia, negative hallucinations, etc., and to respond to posthypnotic suggestions.[30] The purpose of this investigation was therefore (1) to ascertain whether hypnosis effects any reproducible alterations in D.C. potential; (2) if so, to compare these with D.C. records taken (*a*) during sleep and with the subject (*b*) under amobarbital sodium narcosis; (3) to provide a more objective method for determining quantitatively the depth of a trance, and (4) to formulate a new approach which may eventually provide clues regarding the specific physiology involved.

APPARATUS AND TECHNICAL PROCEDURE

Over one year was spent perfecting satisfactory techniques which would yield reproducible results. As has been stated, a portable vacuum tube microvoltmeter had been specifically designed to measure D.C. potentials as pure voltage gradients, independent of current and resistance changes.[31]

The essential characteristics of the Burr-Lane-Nims microvoltmeter are as follows: (1) high input impedance of 10 megohms, so that minimal current (10^{-12} amperes) is drained from the

26. Finesinger, J. E., and Brazier, M. A. B.: The Vulnerability to Drugs of Various Cortical Regions as Evidenced by the Electroencephalogram, Tr. Am. Neurol. A. **70**:151-154, 1944. Brazier, M. A. B., and Finesinger, J. E.: Action of Barbiturates on the Cerebral Cortex: Electroencephalographic Studies, Arch. Neurol. & Psychiat. **53**:51-58 (Jan.) 1945. Cohn, R., and Katzenelbogen, S.: Electroencephalographic Changes Produced by Intravenous Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **49**:560-563, 1942. Derbyshire, A. J.; Rempl, B.; Forbes, A., and Lambert, E. F.: The Effects of Anesthetics on Action Potentials in the Cerebral Cortex of the Cat, Am. J. Physiol. **116**:577-596, 1936. Hoagland, H.; Himwich, H. E.; Campbell, E.; Fazekas, J. F., and Hadidian, Z.: Effects of Hypoglycemia and Pentobarbital Sodium on Electrical Activity of Cerebral Cortex and Hypothalamus (Dogs), J. Neurophysiol. **2**:276-288, 1939. Rubin, M. A.; Malamud, W., and Hope, J. M.: Electroencephalogram and Psychopathological Manifestations in Schizophrenia as Influenced by Drugs, Psychosom. Med. **4**:355-361, 1942.

27. Whitehorn, J. C.; Lundholm, H.; Fox, E. L., and Benedict, F. G.: The Metabolic Rate in "Hypnotic Sleep," New England J. Med. **206**:777-781, 1932.

28. Kubie, L. S., and Margolin, S.: The Process of Hypnotism and the Nature of the Hypnotic State, Am. J. Psychiat. **100**:611-622, 1944. Pavlov, I. P.: Inhibition, Hypnosis, and Sleep, Brit. M. J. **2**:256-257, 1923.

29. Buell, F. A., and Biehl, J. P.: The Influence of Hypnosis on the Tremor of Parkinson's Disease, Dis. Nerv. System **10**:20-23, 1949.

30. Davis, L. W., and Husband, R. W.: A Study of Hypnotic Susceptibility in Relation to Personality Traits, J. Abnorm. & Social Psychol. **26**:175-182, 1931.

31. Standard electrometers used by physicists are difficult to manipulate under ordinary conditions.

organism [32]; (2) high sensitivity (10 to 100 times that of a Compton electrometer; a potential difference of 10 microvolts can be measured); (3) high stability (general unsteadiness at the zero point and random fluctuations are minimal; the instrument remains in balance after many hours of high sensitivity readings); (4) maximum independence of external electrical disturbances (when measuring in the millivolt range, shielding is usually unnecessary for either apparatus or organism); (5) direct reading in microvolts or millivolts (to eliminate subjective

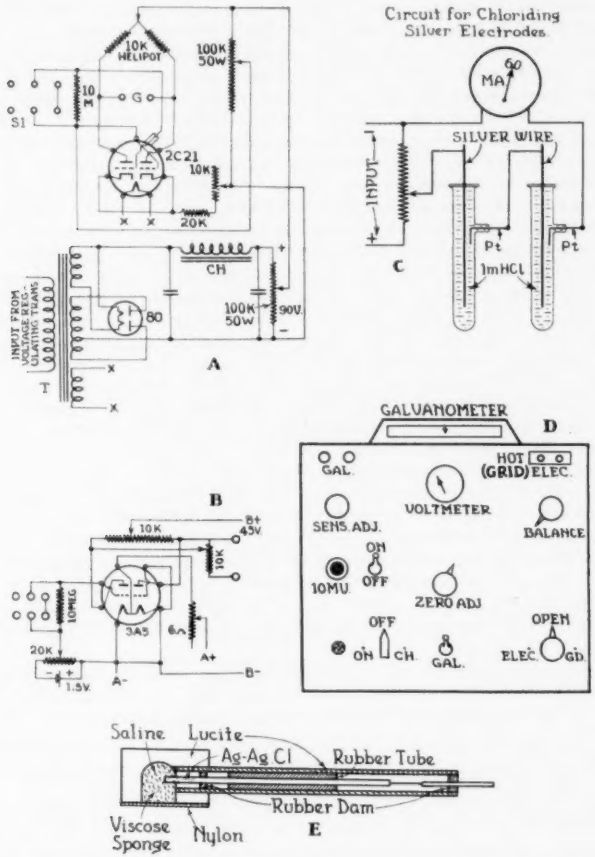

Fig. 1.—*A*, 2C21 combination of A.C.-powered microvoltmeter and photoelectric recorder (after fig. 2, Burr [4b]); *B*, 3A5 D.C. powered microvoltmeter (after fig. 1, Burr [4b]); *C*, circuit for chloriding silver electrodes; *D*, panel of 3A5 instrument; *E*, electrode.

32. Prior to development of vacuum tubes, measuring instruments, owing to their relatively low resistance, acted as an external shunt on the system being measured. Negligible errors were introduced where either the D.C. or standing potential was very high or the recuperative powers of living systems were marked; but in small animals significant disturbances in the electrical output of the living system were produced, as current drains exceeding 10^{-8} amperes theoretically polarize cell boundaries.

judgment of experimenter); (6) determinations independent of current flow and resistance of tested object; (7) utilization of standard radio parts, so that construction costs are kept minimal; (8) portability.[33]

The microvoltmeter is balanced at free grid, for if current flows in the grid circuit an error will be introduced, depending on the polarity of the grid current and that of the system measured. Essentially, a Wheatstone bridge circuit is developed, with a twin tube or two vacuum tubes and fixed resistance used as the third arm in the bridge, with potential differences to be measured placed across 10 megohms on the fourth arm. The bridge is unbalanced by voltage gradients across the 10 megohms, with the resultant plate current changes read on a galvanometer (fig. 1 *B*). Reversible, nonpolarizing silver–silver chloride electrodes were developed, operating in isotonic saline solution. These are made by chloriding pure silver wire or rod in hydrochloric acid. By producing several such electrodes it is possible to obtain a pair differing from each other by less than 1 millivolt. Ultimately, these tend to drift apart; when this occurs irreversibly, a new pair is substituted (fig. 1 *C* and *E*).[34] Holders are molded of lucite, in which is inserted synthetic sponge sealed into the well by a nylon covering. Electrodes are immersed in fresh saline solution and then brought into contact with the living organism, which has been saturated with saline solution at the measuring points, no metal contacting the system being measured. The combination of synthetic sponge and nylon has proved more durable than either cotton or sponge, which may be directly brought into contact with the living system but tends to render less reproducible results, as the continual electrode disturbance necessitated by changing cotton or sponge at least daily seems to help precipitate electrode drift.[35]

In the 3A5 D.C.-powered microvoltmeter, which contains a built-in A.C. charger for the A battery, it is necessary to disconnect the A.C. line before measuring, owing to occasional interference of considerable magnitude, especially in regions where there are numerous A.C. circuits. To check electrode drift, the difference between galvanometer deflection on ground and that on electrode is ascertained; this should be within 3 millivolts. Balance is determined by comparing the voltage differences between open and ground. Electrodes are checked with reference to the zero point every two to four readings. If there is a discrepancy of more than 2 millivolts, the readings are discarded; otherwise, the last reading is corrected. Pressing the 10 millivolt button (fig. 1 *D*) indicates sensitivity which can be set at any value within the limits of the instrument. Electrodes are reversed at least every third or fourth reading, and after each determination if suspect. Infrequently, television and FM broadcasts produce serious interference, in which case electrodes do not ordinarily reverse.[36] When this occurs, testing is conducted in a shielded cage. In spite of such occasional disturbances, it is usually best not to ground the instruments, as grounds tend to conduct current into the machines at unpredictable times. Occasional electrostatic charges in the surrounding atmosphere may be combated by grounding the electrodes to the instrument.

After experimenting with various electrode placements, it was felt that the most consistent and reproducible results from spot determinations could most easily be effected by summating a bilateral series of four potential differences between head and anterior chest wall:

Grid Electrode		Ground Electrode
Right temporal region	.....1.....	Right chest, midclavicular line
Right temporal region	.....2.....	Left chest
Left temporal region	.....3.....	Right chest
Left temporal region	.....4.....	Left chest

Such a combination tends to wash out any errors in single determinations. The important factor, however, is relative change in potential difference, and not absolute magnitude. Living

33. Burr and others.[1] Northrop and Burr.[24f]

34. Dr. Theodore Shedlovsky, of the Rockefeller Institute, suggested dipping carefully cleaned pure silver wire in molten chloride until the temperature gradient between them is equalized. Wire removal leaves the silver chloride coating. Repeated wire dippings produce more rugged electrodes, a small portion of which is left exposed to the enveloping saline solution.[1b] This may be used in conjunction with the electrolytic deposition of silver chloride.

35. Electrode drift may sometimes be combated by gently cleaning or scraping the electrode tips.

36. Living systems act as crystal rectifiers, converting external radiations, particularly of very high frequency, to D.C. current.

systems are fluid; in fluid systems isopotential points are meaningful only when measured against a reference point (which in itself may be changing). This was pointed out by Willard Gibbs many years ago. Presumably, the changes in such systems are primarily associated with ions; therefore, potential measurements of living systems show only the relation between two parts of the system, in contrast to the material universe, where a potential at a point is defined as the energy necessary to transport a unit charge from infinity to the point in question.[37]

It was ultimately decided to attempt more quantitative determinations, using a combined Burr-Lane-Nims A.C.-operated microvoltmeter and General Electric photoelectric recorder. This instrument consists of a twin triode, 2C21 (1642), employing a cathode follower in a bridge circuit. The cathode follower resistance is variable, and the control grid can be balanced at free grid potential by means of a double pole, double throw input switch—a mandatory condition of operation. A standard power pack, which must be operated in conjunction with a voltage-regulating transformer, supplies power to the bridge. Output from the plates is fed to the photoelectric recorder, with a 3 microampere, full scale deflection, whose galvanometer has approximately a 10,000 ohm critical damping resistance. A 10,000 ohm potentiometer is used to calibrate the apparatus, with which any desired number of millivolts can be introduced into the microvoltmeter and recorded by pen movements. The sensitivity can be set as high as 1 millivolt per unit deflection (or any multiple thereof) by interposing the potentiometer between the bridge output and the galvanometer input. As with the D.C.-operated microvoltmeter, no current is drawn from the living system, and the recorder can be used as a straight deflection instrument—null point determination being unnecessary (fig. 1*A*). Electrode connections to the instrument and of the instrument to the recorder are arranged so that when the pen is deflected to the right of the zero point the grid electrode will be positive to the ground electrode by the imposed number of millivolts, and vice versa. As with the D.C.-operated recorder, it is usually unnecessary to ground any part of the apparatus except when there is considerable electrical interference, especially alternating current, in the environment. The recording paper may be set at either 1 inch (2.5 cm.) per minute or 1 inch per hour.[37a]

When this instrument is used with one pair of leads, the most satisfactory placement yielding the most significant results was placement of the grid electrode anywhere on the forehead and the ground electrode on the palm of either hand.[38] An elastic band or rubber bathing cap was used to hold the head electrode in place—part of a rubber glove for the hand electrode.[39] Pads soaked in saline solution were placed under each electrode to keep the area moist; to minimize drift, the instrument should be turned on several hours before use.

VARIABLES

Although relatively simple when mastered, the technique described is highly specialized and requires considerable experience before reproducible results are achieved. Being extremely sensitive, the instruments must be handled with considerable understanding. Differences in electrode pressure, although they produce errors in measurement, particularly over bony prominences, do not cause significant alterations if care is taken. Temperature variations can significantly change the standing potential difference; however, the modification is sufficiently small to be lost in the results of other variables and can be safely ignored when working in the millivolt range. Skin temperature differences modify the stand-

37. Burr, H. S.: The Meaning of Bio-Electric Potentials, Yale J. Biol. & Med. **16**:353-360, 1944.

37a. Burr.[4b] Langman and Burr.[18b]

38. To date, no satisfactory results have been achieved by bracketing any portion of the cephalic region; at the sensitivity used in these experiments, one electrode must be outside the field being measured.

39. Thoracic movements during respiration tend to produce artefacts when an electrode is strapped to the chest.

ing potential in the ratio of 2.5 C. per millivolt.[40] Even changes in blood flow produce alterations which are within the standard error of measurement. Presumably, the only variables which can significantly alter standing potential magnitude are those found in the biological activity of the entire system or in the region bracketed by electrodes.[40]

Thus, aside from individual variations in checking objectivity of readings, there is sufficient evidence to assume, both theoretically and operationally, that potential differences as measured by these instruments represent electrical properties of the organism, and not artificially introduced artefacts.

TECHNIQUE OF HYPNOSIS

Recordings were taken before, during and after hypnosis, utilizing Erickson's technique.[41] After preliminary discussions with the subject, a long series of carefully graded suggestions was given whereby the question of a trance, first as a remote and distant state—a possibility which might sooner or later come about—was raised. Thus, sleep was first suggested as a remote possibility and was gradually brought closer to the immediate situation while introducing a still further progressive step of actual sleep. The subject was hypnotized in such a fashion that he actually participated in the entire process, becoming interested in his sensations as intrapersonal experiences. Whenever possible, the idea of sleep was linked up with motor behavior; e. g., as his hand rose, he would become increasingly sleepy until when the hand finally touched the face he would close his eyes and go to sleep. This gave the subject the choice of lowering the head or bringing up the hand; such a procedure relates hand movements and sleep, and the closer the hand approached the face, the more the subject realized "I'm getting there," proof of which stemmed not from the physician's words but from his own experience of having the hand in that particular position and his total awareness that the hand was close to the face. Those who were able to become cataleptic were told to signify that they were sleeping deeply by lowering the hand, which would not reach the lap until the subject was ready.

Subjects often have much difficulty in recognizing whether they are awake or asleep. Therefore, on first being hypnotized, they were given sufficient time to realize that they could sleep deeply and continue to hear some one speak.

Direct commands were avoided as much as possible, not only to allow time for proper neurophysiological and psychophysiological orientation, but also because commands imply execution; if a command is not executed, the subject has been taught to fail. During the first hypnosis, conditioned reflexes were established to facilitate subsequent induction and termination of trances.

RESULTS OF INVESTIGATION

With the previously described instruments, 60 standing potential records were taken of 20 subjects[42] during hypnosis, and 17 records, of 13 subjects[43] under amobarbital sodium narcosis (0.35 to 0.5 Gm. of the drug given intravenously). Four of these subjects were hypnotized, given amobarbital, and again hypnotized. Although results of spot determinations were sometimes equivocal (e. g., fig. 2,

40. Burr, H. S.: Variables in D.C. Measurement, Yale J. Biol. & Med. **17**:465-478, 1945.

41. A technique learned when I was a student of Dr. Milton H. Erickson, 1945-1946, Wayne University College of Medicine.

42. Seven women and 13 men from 23 volunteer candidates. The three who could not be hypnotized presented rigid, unmodifiable behavior patterns (two men and one woman); two were somewhat antisocial and led relatively isolated existences. All subjects were university students and professional people.

43. Three women and 10 men; two of the nonhypnotizable candidates underwent narcosis.

L. L. and *A. M.*),[44] continuous EMF tracings, obtained with the combined microvoltmeter and photoelectric recorder at a speed of 1 inch (2.5 cm.) per minute, seemed to provide a reliable quantitative index of trance depth. During hypnosis the tracing became more regular, and potential difference either gradually increased or decreased in magnitude. At termination of the trance there was usually a dramatic shift in voltage and the tracing eventually returned to that of the normal waking state (fig. 3). Catalepsy, when used to induce hypnosis, sometimes produced marked changes in potential difference (figs. 3 and 6 *B* and *C*). When this occurred after the trance had been established or when the subject voluntarily raised an arm, minimal changes were recorded (fig. 8 *B*).[45]

Figure 4 (*A* and *B*) illustrates differences between trances in the same subject on two occasions. The waking potential difference varied from 29 to 41 millivolts on November 19 (*A*) but prior to termination of hypnosis it had dropped to 12 millivolts. The subject (K.K.) awakened within three minutes after the signal had been given; during the following three minutes he tended to drift off again, then appeared fully awake and alert. Minimal body movement accompanied the transition from hypnosis to the waking state. The posthypnotic record stabilized at about 30 millivolts.

On December 17 (*B*) the subject's waking potential difference was considerably lower, ranging from 6 to 12 millivolts. Catalepsy this time produced an initial rise of 8 millivolts. Prior to speaking of a dream, the potential difference had fallen to 3 millivolts and, as in the previous record, assumed a straight line configuration. When the subject spoke spontaneously of the dream which occurred a few minutes before, the tracing showed an abrupt increase in voltage, and, although he remained seated with his eyes closed, the pattern now could not be distinguished from that characteristic of a waking state. The subject felt that he was in the deepest trance while dreaming (before spontaneous discussion). This correlates with the fact that subsequently his potential difference never dropped to the level it had attained before speaking. In neither trance was there any evidence of posthypnotic amnesia. K. K. could not assess depth of the second trance relative to the first.

Figure 5 *A* shows a grossly unstable tracing following the first trance. At this time, M. A. became extremely loquacious and excited, acting as though intoxicated. The shift in voltage was so great that the pen writer went off scale; the total potential difference could not be determined, and for this reason no base line is indicated. The second trance was considerably lighter; the tracing seldom became smooth; yet even in this instance there was an increase of 43 millivolts at termination of the trance, after which the subject felt sleepy and tired. This time the record was considerably more stable, although, owing to the lack of a base line, comparison with the original prehypnotic record cannot be made.

D. P. (fig. 6 *A*) attempted autohypnosis, which he felt was equivocal. There was no discernible change in potential difference except for continued decrease in voltage. This is one of the three tracings which crossed the base line. During hypnosis, the head, which in all measurements had been positive to the palm in the waking state, became increasingly negative to the palm,[46] and the record smoothed. At termination of hypnosis there was a 28 millivolt shift. Within three minutes the subject was awake but considerably sleepier than before hypnosis. He then vacillated for a few moments between drowsiness and alertness. This correlates with subsequent decreases and increases in voltage (cf. fig. 4 *A*, *K. K.*).

In figure 6 *B*, there was an increase in potential difference of 29 millivolts at induction of the trance. As in the previous record, relatively fast high voltage waves were present during a

44. A daily rise or fall of normal electromotive force tended to alter the corresponding hypnosis or narcosis potentials and on occasion masked the changes relative to the waking state. In addition, continual application of wet electrodes sometimes decreased the effectiveness of trances.

45. Ravitz, L. J.: Electrometric Correlates of the Hypnotic State, Science **112**:341-342, 1950.

46. On an absolute basis, the voltage increased (cf. fig. 2, *D. P.*). Here records on the same subject were made via head-chest spot determinations.

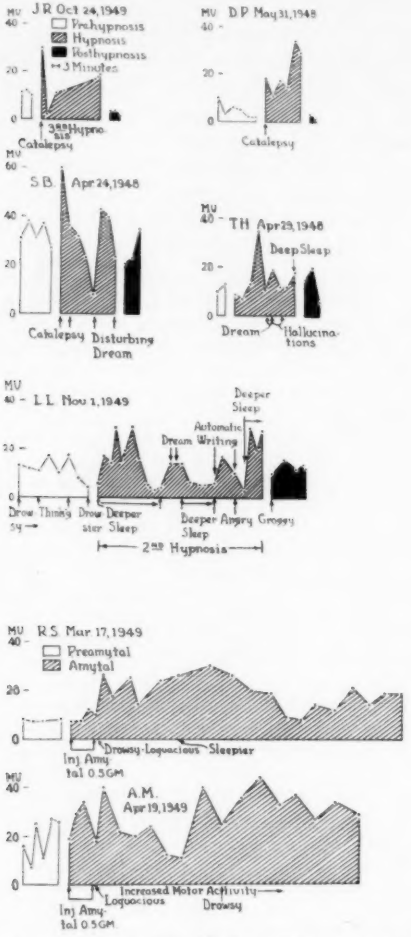

Fig. 2.—Head-chest spot determinations of hypnosis and narcosis.

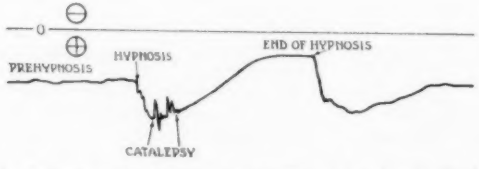

Fig. 3.—Schematic D.C. record of hypnosis (after fig. 1, Ravitz [45]).

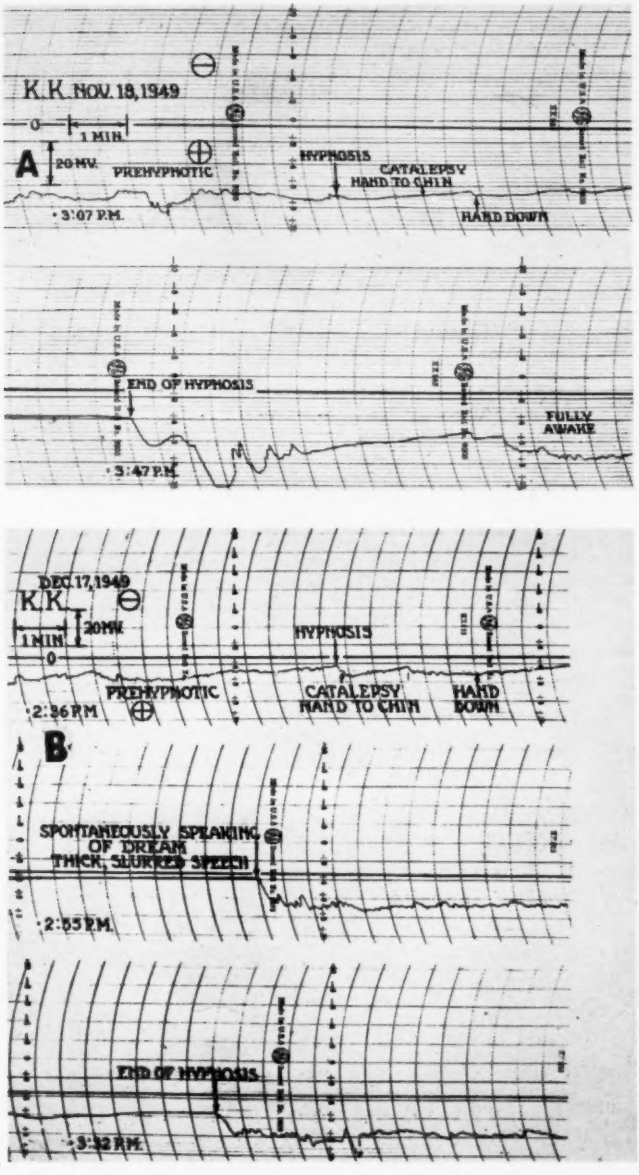

Fig. 4.—*A*, hypnosis record (K. K.); *B*, hypnosis record (K. K.) one month later.

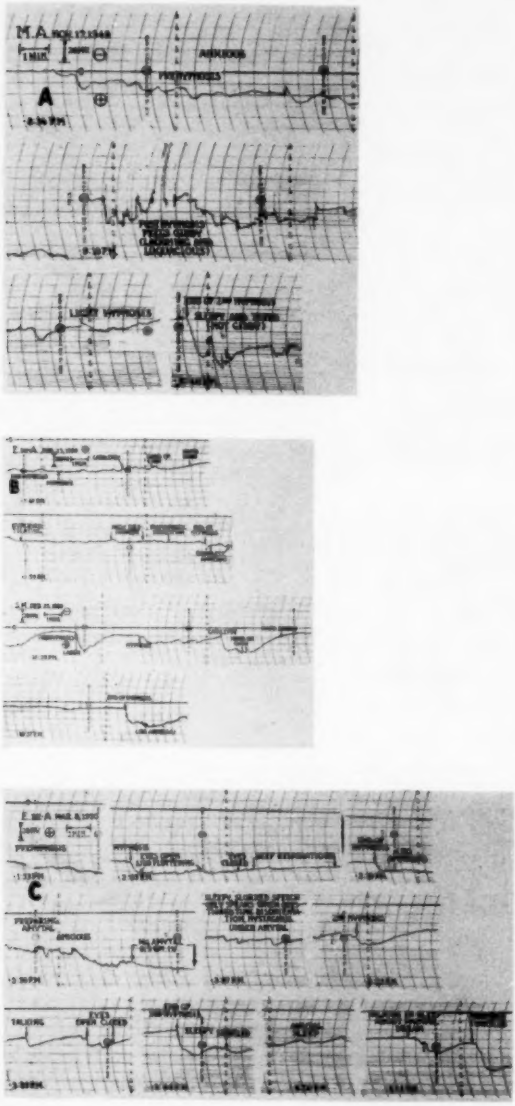

Fig. 5.—*A*, hypnosis record (M. A.) showing effects of emotions on potential difference following trance; *B*, hypnosis records with (E. de-A.) and without (S. M.) amnesia; *C*, records (E. de-A.) during hypnosis, hypnosis under amobarbital sodium narcosis and sleep.

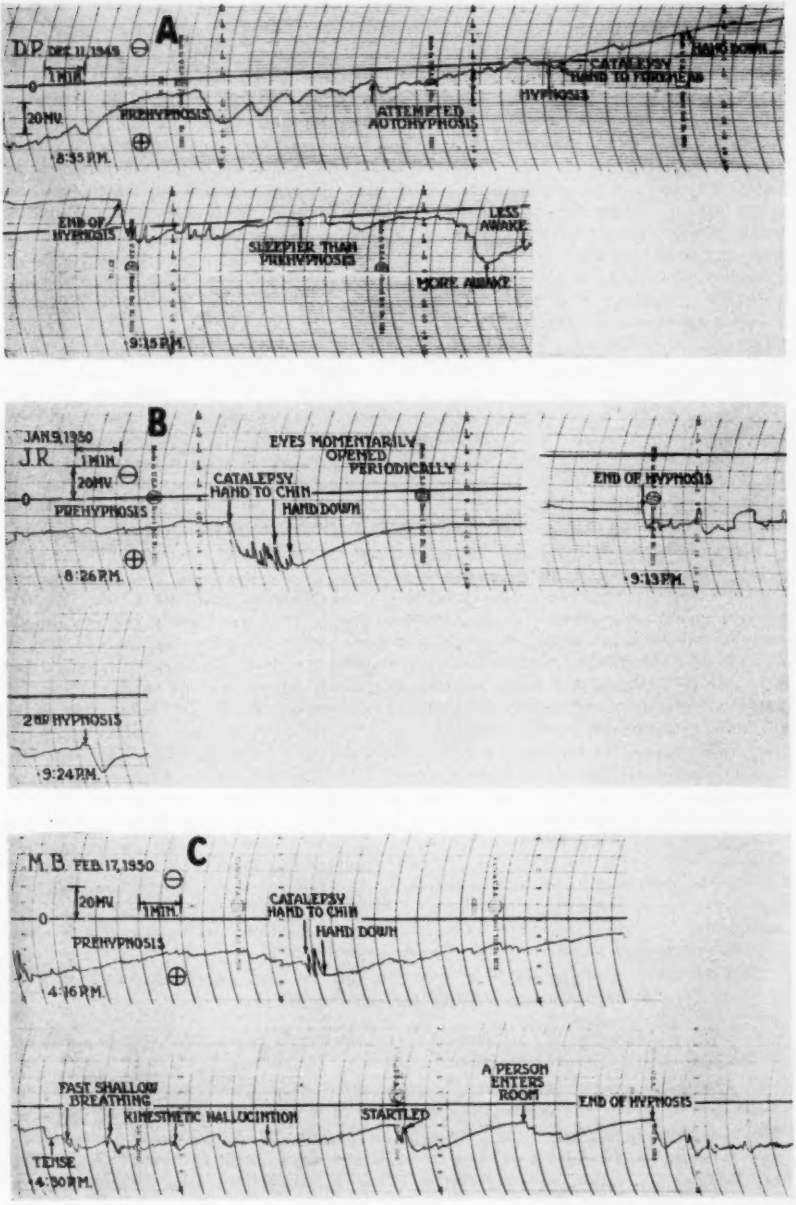

Fig. 6.—*A*, hypnosis record (D. P.) showing decrease in potential difference to negative values; *B*, hypnosis record (J. R.) showing changes in potential difference during induction; *C*, hypnosis record (M. B.) showing changes in potential difference during induction.

transition phase (D. P. [fig. 6 *A*] showed a similar configuration at termination of the trance). The initial increase was followed by a decrease in voltage, and then by a gradual increase, until by the end of hypnosis the potential difference was 32 millivolts, as compared with 16 millivolts prior to hypnosis. A less dramatic shift occurred after termination than with induction.[47] J. R. displayed some conscious resistance to going into a second trance; this time, a relatively small shift of 16 millivolts, unassociated by fast high voltage waves, occurred.

M. B.'s record (fig. 6*C*) showed some shift in voltage with catalepsy; her trance then gradually became deeper until she suddenly appeared tense and began to hyperventilate. At this point, the record approached that of the waking state. She had desired to experience sensations of the building shaking; this was therefore suggested to her.[48] When startled, a configuration similar to that at induction appeared. The subject then continued going into a deeper trance until interrupted by a third person's entering the room. By the end of the hypnosis, the potential difference had fallen to 12 millivolts and then eventually shifted to 34 millivolts, which approximated her prehypnotic level. M. B. had no amnesia except for possible fantasies accompanying tenseness and hyperventilation.[49]

E. de-A. (fig. 5*B*) had a waking potential difference of 50 millivolts, which during the deepest portion of the trance (just prior to hyperventilation) decreased to 35 millivolts. There was only a 10 millivolt rise on termination of the trance—the tracing leveling off at 42 millivolts—approximately the same voltage as during the terminal trance state, but with the mildly rocky base line usually associated with waking records. Despite these minor fluctuations, E. de-A. had complete amnesia after the trance and felt compelled to examine minutely a writing pad, which had been suggested to her, in contrast to S. M. who, though she had an increased potential difference of 24 millivolts during induction of the trance and a 28 millivolt shift at termination, had no amnesia and would, in general, have made a poor experimental or therapeutic subject.

Figure 5*C* shows a later record for E. de-A., whose 60 millivolt potential difference prior to hypnosis increased to 72 millivolts during induction; by termination the potential difference had decreased to 50 millivolts, later stabilizing at 60 millivolts again. This time, however, an embarrassing posthypnotic suggestion had been made: The subject was to inspect carefully the brass buttons on a visiting professor's vest. Although she felt some compulsion to gaze at them, E. de-A. laughingly stated that she felt it would have been indecorous to carry out the suggestion on a man of such renown and for this reason did not have an amnesia. While the preparation of amobarbital sodium was being made before her, the subject became anxious; at this time the potential difference increased from 35 to 60 millivolts. After 0.5 Gm. had been given intravenously, she became very sleepy, closed her eyes and spoke only when questioned. Speech was slurred; the subject was disoriented as to time and displayed nystagmus. Many economic fantasies were elicited. By the time a second hypnosis was attempted, the potential difference had decreased to 36 millivolts. The second trance (under amobarbital) produced an initial rise of 9 millivolts, followed by a decrease until she began to speak. In this instance, suggestion for opening the eyes seems to have disturbed the trance pattern. By the end of hypnosis the potential difference had decreased to 22 millivolts; there was then a 28 millivolt upsurge, the record stabilizing at 45 millivolts. Next, the subject was allowed to go to sleep; the potential difference again decreased to 28 millivolts. Suddenly she began mumbling about a painful dream which was occurring at the time; this produced an 18 millivolt increase. When she was awakened, a precipitous 30 millivolt rise occurred, and the pattern stabilized at 60 millivolts. Her hypnosis and sleep tracings appear identical.

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47. Compare figure 2, *J. R.* This shows the precipitous initial increase, followed by a decrease and a gradual increase in potential difference.

48. The question has been raised by Lyman as to whether this was a true vestibular hallucination (with kinesthetic components) in view of her anxiety and the strong subjective effect of unpleasant external reality influencing her (Lyman, R. S.: Personal communcation to the author). M. B. claims that she is normally sensitive to slight movements of the building. This has implications regarding further effects of such phenomena on her, the existence of which has not been determined.

49. Subject described with great vividness how she saw a slit of light approaching her during induction of trance; she now sometimes uses this fantasy to induce regular sleep.

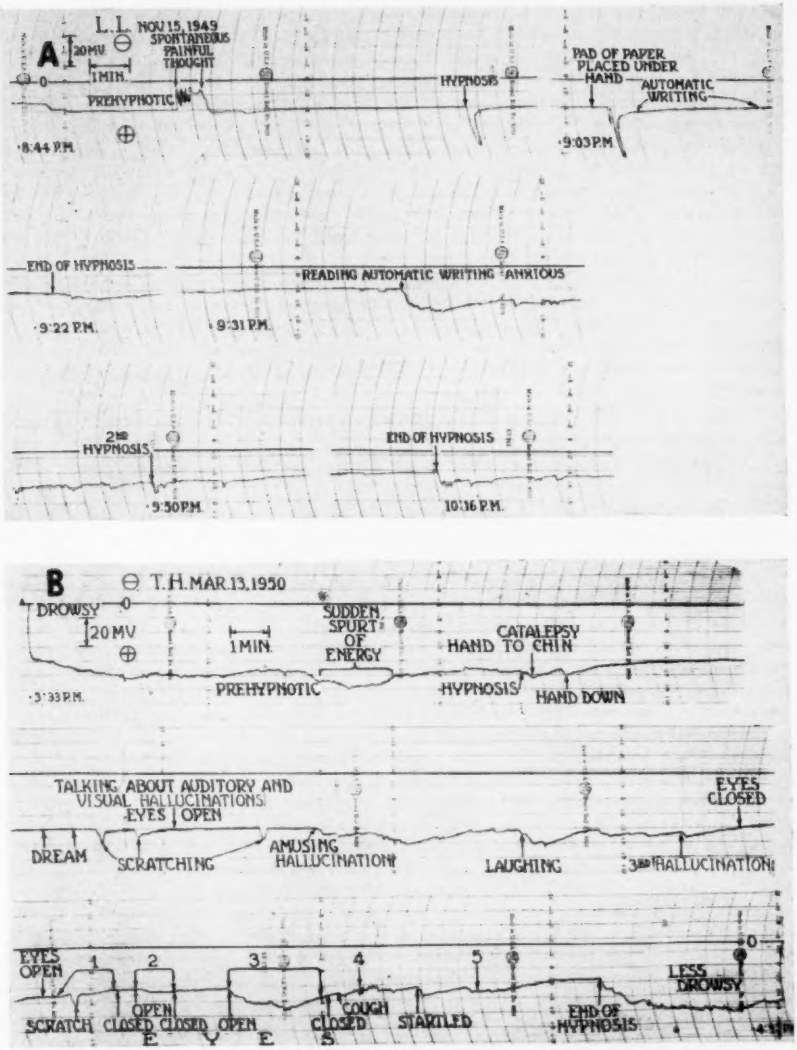

Fig. 7.—*A*, hypnosis record (L. L.) showing effects of anxiety; *B*, hypnosis record (T. H.) showing effects of visual and auditory hallucinations, regressions, anxiety and grief. *1*: regression to March 1932: subject reports argument with classmate to third grade teacher; *2*: regression to June 1941: subject reports slight anxiety regarding graduation speech to sister: *3*: regression to May 23, 1946: subject very upset and anxious at leaving good friend; *4*: spontaneous painful thoughts about previous situation; *5*: attempt to elicit previous anxious thoughts.

L. L. (fig. 7 *A*) was the only subject whose smooth waking pattern was similar to that seen in hypnosis and sleep. The prehypnotic potential difference was 20 millivolts. Spontaneous development of painful thoughts was associated with fast high voltage waves (there was no discernible movement). With induction of hypnosis there occurred an initial 24 millivolt spike; another spike developed before writing, although these may have been artefacts. There was no change in potential difference with automatic writing. At the end of hypnosis the potential difference had fallen to 14 millivolts; termination produced a 5 millivolt increase, to the prehypnotic level except that the tracing was now more irregular. The anxiety mobilized when the subject attempted to translate his writing is indicated by a 15 millivolt increase.

The second trance caused a smoothing of the tracing and an 8 millivolt decrease. During both trances the subject displayed considerable hostility and resentment, feeling that, by the tone of the physician's voice, his efforts were not appreciated. For this reason, he believed that the trances were very light (cf. fig. 2, *L. L.*).[50]

At the time T. H. suddenly became energetic (fig. 7 *B*) there was a 10 millivolt increase in potential difference. No changes occurred in the hypnosis tracing during a dream or the discussion of auditory and visual hallucinations with eyes open (the subject was watching a dance) until an amusing incident was suggested; this caused irregularity and voltage increase. Scratching and coughing also produced rises in potential difference. The subject was then regressed:

1: March 1932: At this time T. H. reported an argument with a classmate to his third grade school teacher.

2: June 1941: The subject reported slight anxiety regarding a graduation speech to his sister.

3: May 23, 1946: The subject was greatly upset and grief stricken at leaving a good friend. This was associated with irregularity and a 14 millivolt increase. It is of interest to note that in this instance T. H. specified an exact date.

After this (*4*) there occurred spontaneous painful thoughts about the previous situation. This produced a pattern similar to that of L. L., although of lower voltage (cf. fig. 7 *A*). There was then an attempt to induce previous anxious thoughts (*5*). However, emotional impact was diminished, and the accompanying change in potential difference was barely discernible. By the end of hypnosis the potential difference had decreased from 48 to 24 millivolts[51]; within two minutes it stabilized at the prehypnotic level of 46 millivolts, with increased irregularity, however. T. H. was considerably less drowsy at the end of the experiment than at the beginning.

J. O. (fig. 8 *A*) was apprehensive prior to hypnosis, her prehypnotic record fluctuating between 34 and 76 millivolts. Just before her eyes closed, the subject laughed briefly, after which there was a 14 millivolt increase. The record then became more regular, showing a slight rise in potential difference to 40 millivolts until a pad was placed under her hand prior to automatic writing. A 28 millivolt increase occurred at this point, followed by an unstable tracing during the procedure. By the end of hypnosis, the potential difference had increased to 64 millivolts; there was an upsurge of 12 millivolts; the record then dropped to 66 millivolts, differing from her hypnotic record only in configuration. The subject felt that this trance was a very light one, during which she had constantly thought of many things. The posthypnotic tracing was considerably more stable than the prehypnotic tracing in that random voltage fluctuations were now minimal. By the time she was again hypnotized, the potential difference had risen to 83 millivolts. There was again an initial upsurge; by the end of the second trance the potential difference had dropped to 66 millivolts. At termination, the potential difference abruptly increased 26 millivolts and stabilized between 70 and 80 millivolts. The tracing now showed considerable consistent irregularity, in contrast to the record prior to and after the first trance. J. O. was now loquacious, euphoric and excited. It is of interest to note that the potential difference increased during the first trance and decreased during the second, which the subject felt was considerably deeper, primarily because her thoughts were more circumscribed, being focused on her hypnotic state.

50. Subject concluded that the physician, in part, represented his mother. The transference was never completely resolved.

51. Compare figure 2: *T. H.* During this subject's head-chest spot determinations, there was voltage increase.

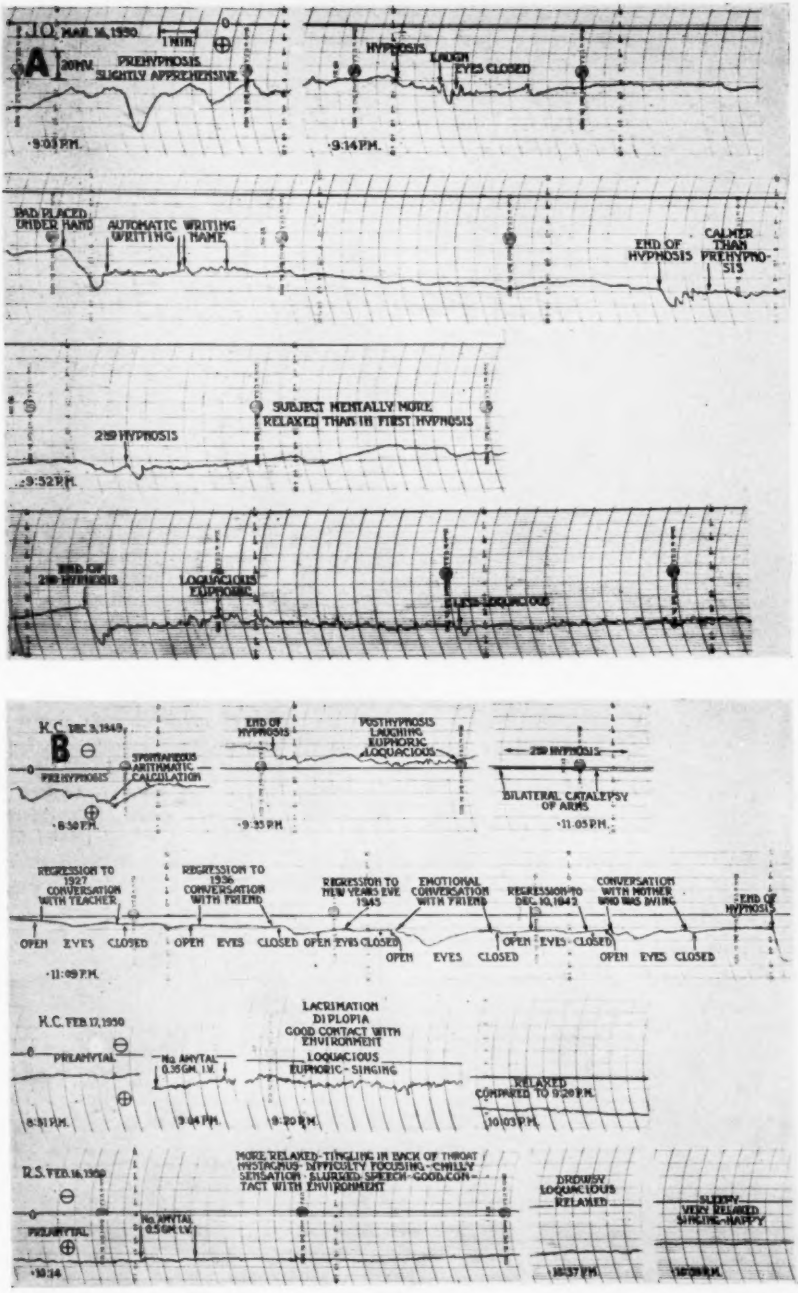

Fig. 8.—*A* (J. O.), effects of emotion following trance; *B* (K. C.), effects of emotion during and after hypnosis and narcosis.

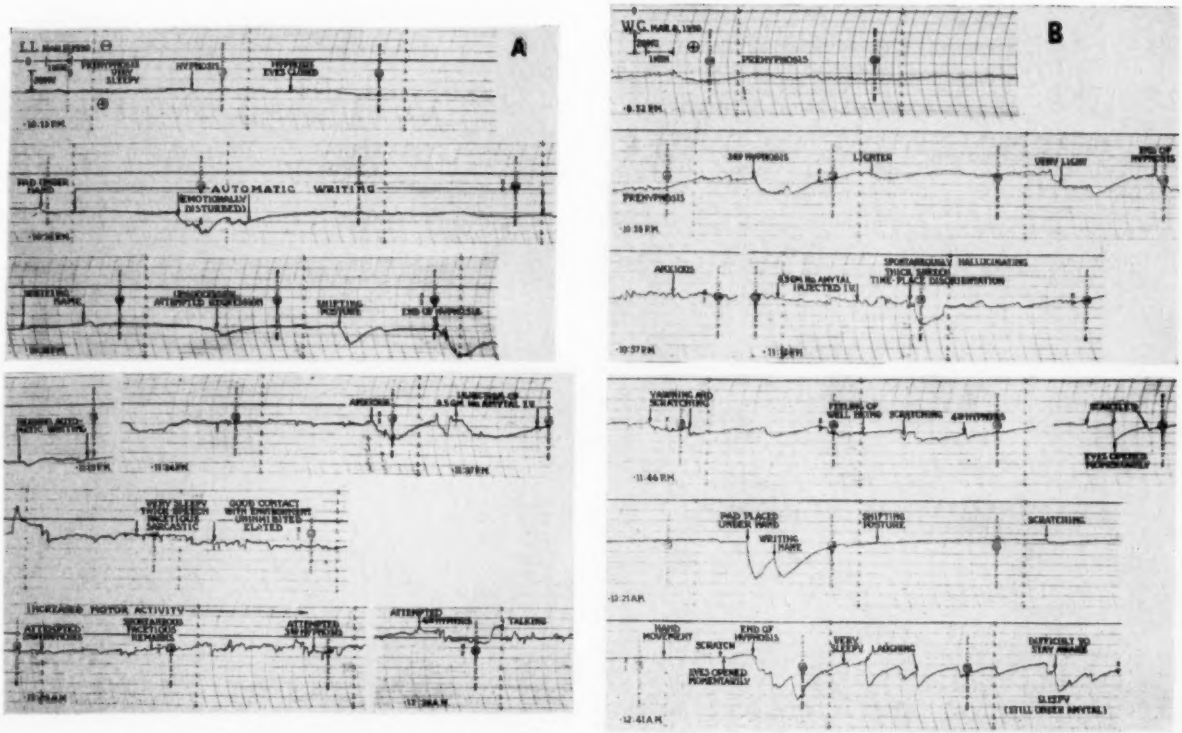

Fig. 9.—*A* (L. L.), mobilization of resistance to hypnosis following narcosis; *B* (W. G.), lowering of resistance to hypnosis following narcosis.

The tracing of K. C. (fig. 8 *B*) changed from + 15 millivolts, prior to the trance, to — 18 millivolts, at the deepest part of the first hypnosis, thus crossing the base line. Only a minimal voltage shift occurred at termination of the trance. When fully awake, the subject became euphoric, loquacious and excited; the tracing assumed an irregularity similar to that of J. O. (cf. fig. 8 *A*) at the end of her second hypnosis. During the second trance, the record shifted to the positive side. Bilateral catalepsy of the arms did not alter the tracing, which showed increasingly positive voltage, nor did regressions with hallucinations and eyes open, until the subject had emotive conversations with a friend—when the potential difference increased 12 millivolts (cf. fig. *7 B, T. H.*)—and with his dying mother. At termination of the hypnosis there occurred a precipitous positive increase of 25 millivolts.

Under amobarbital narcosis, K. C. became loquacious, euphoric and excited; his record again showed the characteristic irregularity seen in J. O.'s tracing during her second posthypnotic state (fig. 8 *A*) and in his own posthypnotic state, described above. Relaxation was associated with smoothing of the tracing; voltage increased somewhat, although not appreciably.

R. S. showed practically no change in potential difference after injection of 0.5 Gm. amobarbital sodium intravenously (fig. 8 *B*), despite development of slurred speech, chilly sensations and eventual loquaciousness, except for a general smoothing of the record and a slight decrease in voltage. Although euphoric, the subject felt relaxed, however, in contrast to J. O. and K. C. (cf. fig. 2, *R. S.*).

L. L. (fig. 9 *A*) again showed a very smooth prehypnotic tracing (cf. fig. 7 *A*). This time, however, voltage increased from 30 to 44 millivolts during hypnosis, in contrast to the trance of November 15, when there was a decrease in potential difference. At one point the subject became noticeably disturbed while writing; this was accompanied with a 22 millivolt increase (cf. figs. 7 *A* and *B* and 8 *B*). A shift in posture seemed to cause a lighter trance. At termination there was at least a 27 millivolt increase, the pen writer going off scale—a much greater shift than that during the trance of November 15. Temporarily stabilizing at 55 millivolts, the voltage eventually decreased to 16 millivolts. The subject felt that this was a much deeper trance than that of November 15, his negative feelings having abated somewhat.

When amobarbital sodium was being prepared, L. L. became anxious, the potential difference increasing 20 millivolts (cf. fig. 5 *C*, taken during amobarbital preparation). Under narcosis, the subject became euphoric, facetious and sarcastic; there was increased motor activity, and the tracing became consistently irregular (cf. fig. 8 *A, J. O.*, and *B, K. C.*) Three attempts were made at hypnosis; at each, L. L. closed his eyes but soon burst forth with some sarcastic remark and opened his eyes. By the persistently irregular pattern, it is obvious that hypnosis was not accomplished. The subject later reported that at this time he felt irresponsible and negativistic. The potential difference gradually decreased, crossing the base line and becoming negative at 12:20 a. m., but eventually stabilizing at the base line until the experiment ended, at 12:38 a. m. (cf. figs. 6 *A, D. P.*, and 8 *B, K. C.*: other tracings which became negative under hypnosis or narcosis).

W. G. was a very resistant subject. Whenever a deeper trance was suggested, he became lighter (fig. 9 *B*), although evidences of a very light trance were present, i. e., initial increase, followed by a decrease in voltage and smoothing of the tracing. He was hypnotized three times prior to injection of amobarbital; indications of deeper and lighter hypnotic states are evident from the record of the third trance. Amobarbital did not appreciably affect the tracing. At first, the subject was disoriented to time and place; at no time did he become euphoric. The subject did not resist the fourth hypnosis. The second time he was startled, there was a 16 millivolt increase; a paper pad placed under his hand likewise caused a positive shift of 34 millivolts, as did his writing his name. Momentary opening of the eyes near the end of hypnosis was associated with a barely discernible change. By termination, the potential difference had decreased from 50 to 32 millivolts; a 42 millivolt increase now occurred. The subject was very sleepy after the trance and tended to doze. This was always associated with a decrease in voltage, the increases correlating with attempts to rouse him (cf. figs. 4 *A, K. K.* and 6 *A, D. P.*). In contrast to L. L., who could be hypnotized prior to injection of amobarbital, but who resisted hypnosis after its administration, W. G's resistance was lowered by the barbiturate.

In figure 10 a record during intense concentration (cf. fig. 7 *B*, *T. H.*) is contrasted with those obtained during complete physical relaxation and under emotional tension. On lines 2 and 3 are shown the effects of coughing, as well as the 37 millivolt shift at the end of hypnosis, the voltage decreasing to 51 millivolts during the trance and stabilizing after hypnosis at 84 millivolts, the prehypnotic level. Amobarbital sodium produced a decrease to 55 millivolts. Under narcosis, the subject remained in good contact with environment and never became euphoric or loquacious. A second trance decreased the potential difference to 40 millivolts at the lowest point (45 millivolts immediately prior to termination); this increased 17 millivolts and became relatively stabilized at 52 millivolts. Thus, in this record the initial trance and drug both decreased the potential difference, which after a second hypnosis induced under amobarbital, decreased still further.

S. T. illustrates high voltage fast frequency waves sometimes associated with anxious or painful thoughts or induction or termination of hypnosis (cf. figs. 6 and 7).

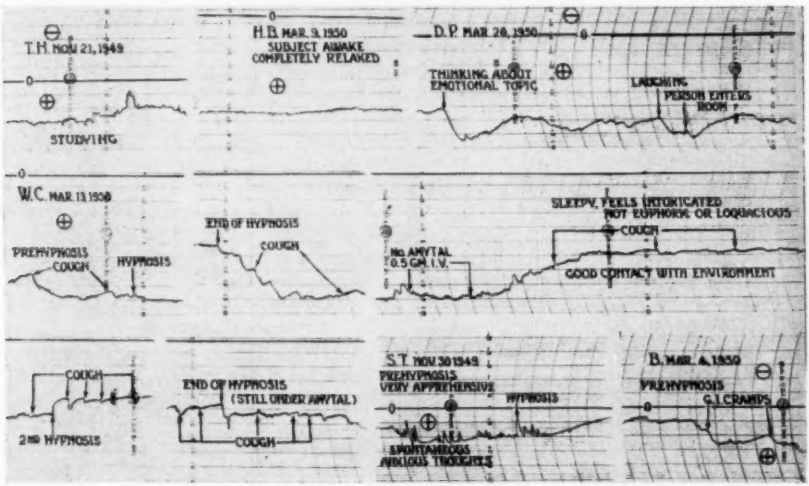

Fig. 10.—Effects of studying, complete relaxation, emotion, coughing and cramps on potential difference record.

Intestinal cramps also cause changes in potential difference, as can be seen in *B*. (These were precipitated by anxiety and eliminated during hypnosis.)

COMMENT

It is evident that hypnotic states produce characteristic alterations in potential difference without regard to sex. Some subjects like to have the trance occur and terminate rapidly; some like slower transition periods, and others vary in this respect in different situations. This variation can be seen on the records. Unless the waking record was smooth, sitting with the eyes closed did not produce such a tracing until the subject was in a trance or asleep. Depth of hypnosis, as measured electrometrically, did not seem to be correlated with ability to develop amnesia or other phenomena frequently necessary for a good therapeutic or experimental trance. Any disturbance of the hypnotic state could be detected immediately by changes in voltage and in configuration of the tracing.[45]

Alterations in potential difference under amobarbital sodium narcosis were less pronounced than those under hypnosis and showed considerable more variation, the potential difference either increasing or decreasing in voltage, remaining about the same or becoming irregular. The latter effect always accompanied euphoria, loquaciousness and general excitability; such tracings could not be differentiated from the posthypnotic configuration associated with similar emotional states.

Various depressants and excitants of the central nervous system, including amobarbital sodium (90 mg. per kilogram) were injected intraperitoneally into white rats and measurements taken with identical instruments. Despite profound physiological disturbance, there was likewise relatively little evidence of any effect of administration of the drug, although amobarbital and secobarbital (seconal*) seemed to decrease slightly the potential gradients.[52] One might assume that, despite marked cortical effects of barbiturates, as measured by the electroencephalogram, in contrast to hypnosis, at the sensitivity used, the former does not always produce changes in potential difference of the order of magnitude to be found on the surface of the organism, whereas hypnosis does. As might be expected, no consistent results occurred in the four subjects who were hypnotized, given 0.5 Gm. of amobarbital and again hypnotized. In one subject the effects of amobarbital on the potential difference were equivocal, although the second trance showed more decrease in voltage than the first. In another, hypnosis caused an increase in potential difference; with amobarbital the voltage dropped considerably, although the subject became negativistic and refused to be hypnotized again. The third subject was resistant to hypnosis prior to narcosis, and, although amobarbital produced no appreciable changes in potential difference, he was easily hypnotized after injection of the drug, the record developing its characteristic pattern. In the last subject, the first hypnosis caused a decrease in voltage, as did amobarbital; hypnosis following narcosis decreased potential difference still further. For none of these subjects did amobarbital produce a smoothed tracing.

In several records, the subject was startled during the waking state, hypnosis and narcosis. This was always followed by a relatively precipitous increase in potential difference and then by a gradual return to the previous pattern. When this occurred under hypnosis or narcosis, the subject usually reported feeling in a lighter state at the time. Those who were in very light trances momentarily awakened. Although the instruments employed operate independent of changes in current and resistance, this represents the so-called psychogalvanic reflex, for, according to Goadby and Goadby,[53] such responses have both resistance and potential components. Further investigation may indicate that this furnishes another index of trance depth.

Sleep and hypnosis produce similar alterations in direct current,[54] even when electrode placements are between the pubic symphysis and the vagina,[55] in that

52. Burr, H. S., and Smith, P. K.: The Relationship Between the Bio-Electric Potential of Rats and Certain Drugs, Yale J. Biol. & Med. **11**:137-140, 1938.

53. Goadby, K. W., and Goadby, H. K.: The Nervous Pathway of the Psycho-Galvanic Reflex, J. Physiol. **109**:177-184, 1949.

54. Earlier studies indicated no D.C. alterations during sleep, although at this time zinc electrodes were used, which produced some back electromotive force; also electrode placement differed from that used in later experiments (Davis, H.; Davis, P. A.; Loomis, A. L.; Harvey, E. N., and Hobart, G.: A Search for Changes in Direct-Current Potentials of the Head During Sleep, J. Neurophysiol. **2**:129-135, 1939).

(Footnotes continued on next page)

they both cause a gradual alteration of characteristic waking patterns to a smoothed configuration. However, although sleep is always accompanied with a decrease in voltage,[56] hypnosis may cause either a decreased or an increased potential difference. A subject may have a decrease during one trance and an increase in another. As has been stated, only relative change in potential difference, and not absolute magnitude, is of significance. Thus, the only factors which seem to be correlated with depth are the magnitude of relative voltage change (whether increased or decreased) from that of the waking pattern [57] and the amount of smoothing.

There are few guides to the geometry of electrode placement, which was established on a trial and error basis. At the sensitivity used, one electrode had to be at some point other than the head; cephalic bracketing produced no striking results. The fact that the potential differences between head and palm are far greater than those between various cranial points may partially account for greater relative alterations detected at these spots.[58] Although other placements might yield similar results, experimentation with all possible loci was beyond the scope of this investigation.

With all subjects studied, the head was always positive to the hand in a waking state; in only three instances did the tracing cross the base line, the head becoming negative to the palm. Head-chest placements do not display this consistency as regards polarity and are of considerably lower voltage.

Many studies have been made of electrolyte balance, ionic transport and similar chemical processes, in the hope that they might yield significant evidence as to the source, meaning and significance of potential differences, although it is still obscure as to what chemical entities either give rise to or modify these differences. Such phenomena can be partially explained by known initial differences in electrolyte concentrations and by ionic motility across phase boundaries, as it is generally accepted that membrane potentials at these points are a consequence of differences in electrolyte concentrations on the two sides of the boundary. In nonliving systems, this potential approaches zero as ionic equilibrium is reached. Yet, although cell chemistry is of major importance, attempts to explain potential difference on chemical grounds alone have thus far resulted in confusion.

Burr feels that potential difference may represent an index of stored energy, as represented by summated boundary potentials—a reservoir from which energy can be rapidly drained to meet the exigencies of activity.[59] Experimental evidence supports the hypothesis that actual fields are being measured. Whatever else they may be, all living organisms which have been examined seem to represent quasi-

55. Burr, H. S., and Barton, D. S.: Steady-State Electrical Properties of the Human Organism During Sleep, Yale J. Biol. & Med. **10**:271-274, 1938.

56. King, C. D.: Electrometric Studies of Sleep, J. Gen. Psychol. **35**:131-159, 1946.

57. In the subjects studied, voltage alterations under hypnosis ranged from 3 to 40 millivolts —the magnitude of terminal shift, from 2 to 43 millivolts.

58. Even though resistance changes are not being measured, Richter believes that increased PD's with head-palm leads are due to the greater number of sweat glands on the palm with their increased sympathetic innervation (Richter, C. P.: Personal communication to the author). However, there is no conclusive evidence to demonstrate what part the sympathetic nervous system plays in this picture.

59. Burr, footnotes 3 and 37.

electrostatic fields, which exhibit a definite pattern of potential difference as a whole. Thus, measurements of potential difference may provide clues not only to the pattern of field force, but also to the energy content of the field. It has been assumed that the chemical reactions of metabolism provide the energy necessary for the living process, which is stored in chemical form within the substance of the protoplasmic matrix and, as living systems are never at equilibrium, is continuously expended. When changes in the external or internal environment stimulate protoplasm into some form of response, greater amounts of immediately available energy are required.[59] The first reaction of any biologic system thrown out of relative equilibrium is to overreact; such mobilization of energy may account for the dramatic fluctuations in potential difference sometimes seen at induction or termination of trances—the system then seeking equilibrium as its energy store is either increased or diminished.

SUMMARY

1. Hypnosis is associated with the following characteristic alterations in direct current without regard to sex:

(*a*) The potential difference tracing smooths, losing its usual waking pattern.

(*b*) There is either a gradual increase or decrease of mean potential difference, which may vary in the same subject at different times.

(*c*) Induction when associated with catalepsy sometimes causes considerable increases in voltage.

(*d*) Termination usually results in dramatic positive shifts in voltage, after which the record eventually returns to the waking pattern.

(*e*) Speaking and eyes open do not affect the typical hypnosis record except in subjects who are in very light trances, in which case the tracing assumes a waking state configuration.

(*f*) Dreams, hallucinations and regressions do not alter the typical tracing unless associated with strong emotions.

(*g*) Intense emotions, such as anxiety and grief, cause changes in potential differences, as do scratching, coughing, startle responses and gastrointestinal cramps in waking as well as in hypnoid states.

(*h*) Euphoria, loquaciousness and general excitability following hypnosis produce a consistently irregular pattern, similar to that effected by narcosis when associated with similar states.

2. Comparison of hypnosis records with records of other states reveals certain similarities and differences:

(*a*) When they decrease in voltage, D.C. hypnosis records cannot be distinguished from D.C. sleep tracings. Drowsy states cause a decrease in potential difference.

(*b*) Amobarbital (amytal sodium®) narcosis seems to produce less dramatic records unless associated with general excitability (item 1 *h*); voltage shifts of considerable magnitude which sometimes accompany induction of hypnosis are seldom present, and the gradual wearing off of the drug effect precludes any considerable terminal shifts in voltage.

(*c*) Resistance to hypnosis may be lowered or mobilized under narcosis.

3. Depth of hypnosis, as measured electrometrically, does not appear to be correlated with ability to develop amnesia or other phenomena frequently necessary for good therapeutic or experimental trances, but only with the magnitude of relative change in voltage (whether increased or decreased) from that of the waking pattern and the amount of smoothing. Any disturbance of the hypnotic state can be detected immediately by changes in voltage and in tracing configuration. Thus, a new approach has been formulated by means of which it seems possible to measure objectively changes in depth of hypnosis.

4. The specific physiology is unknown; there is no conclusive evidence to demonstrate what part the sympathetic nervous system plays in this picture. It is felt, however, that potential difference measures one aspect of quasielectrostatic field phenomena, which may represent summated potentials of the bimolecular layers surrounding cells.

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VISUAL AND MOTOR CHANGES IN PATIENTS WITH MULTIPLE SCLEROSIS

A Result of Induced Changes in Environmental Temperature

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CLIMATE and temperature have been recognized as affecting the incidence of multiple sclerosis. Although sex and race appear not to be important factors in its occurrence, its geographical distribution seems to vary significantly with the distance of an area from the equator. According to one study of the mortality statistics in 14 countries,[1] there is "'an inverse and rather striking relationship between reported mortality due to multiple sclerosis and mean annual temperature. The colder the climate, the higher the crude death rates for multiple sclerosis." Other authors have been in agreement,[2] pointing out the commonness of multiple sclerosis in northern European countries, as well as Canada, the United States and Australia. In Canada, the United States and Italy, the areas with a higher death rate from multiple sclerosis seem to lie above the 60 degree isotherm of the mean annual temperature reduced to sea level.

A definite statistical relationship of multiple sclerosis to seasonal variations in temperature does not seem to exist.[1] However, the statistical prevalence of this disease in colder areas may depend on many factors other than temperature.

From material gathered from questioning patients, Simons [3] observed that heat caused an increase in the symptoms of weakness and spasticity, whereas cold seemed to have no worsening effect. Chilling, too, has been regarded as one of the common precipitating factors in the disease.[4] In support of a theory that vasoconstriction is the basis for multiple sclerosis, heat has been incriminated as causing some of the brief, sudden episodes in its symptomatology.[5] The forms of heating referred to were a hot bath, hot soup and a hair dryer.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Limburg, C. C.: The Geographic Distribution of Multiple Sclerosis and Its Estimated Prevalence in the United States, A. Research Nerv. & Ment. Dis., Proc. (1948) **28**:15, 1950.

2. Brain, W. R.: Critical Review: Disseminated Sclerosis, Quart. J. Med. **23**:343, 1930. Steiner, G.: Multiple Sclerosis: Etiological Significance of Regional and Occupational Incidence, J. Nerv. & Ment. Dis. **88**:42, 1938. McAlpine, D.: The Problem of Disseminated Sclerosis, Brain **69**:233-250, 1946.

3. Simons, D. J.: A Note on the Effect of Heat and of Cold upon Certain Symptoms of Multiple Sclerosis, Bull. Neurol. Inst. New York **6**:385, 1937.

4. Schumacher, G. A.: Multiple Sclerosis, J. A. M. A. **143**:1059 (July 22) 1950.

5. Brickner, R. M.: The Significance of Localized Vasoconstrictions in Multiple Sclerosis, A. Research Nerv. & Ment. Dis., Proc. (1948) **28**:236, 1950.

There is, then, a traditional tendency to regard both heat and cold as precipitating or worsening factors in this disease. In questioning an unselected group of 10 patients with multiple sclerosis on a male neurology service in a large Veterans Administration hospital, there proved to be an 80 per cent incidence of intolerance to bathing in hot water. Generalized weakness was described as the reason for avoiding such baths. With the realization of an apparent clinical paradox, that a hot bath was reported to have a deleterious effect in patients having a disease with a higher incidence in colder climates, it was felt that the validity of this observation should be subjected to experimental testing. Accordingly, this group of 10 patients with multiple sclerosis and a control group of 10 patients with other neurological diseases underwent total and partial immersion in hot, tepid and cold water, and the changes in certain symptoms and testable performances recorded. Further examinations were carried out, using fever cabinets and various mechanical and chemical agents, in an attempt to elucidate further the effects of induced temperature changes.

MATERIAL

Comprising the multiple sclerosis group were 10 white men, 20 to 40 years of age, for all of whom the history, physical findings and laboratory studies were typical of this disease. No patient was included about whom there was any question of differential diagnosis. In a classification according to the duration of their disease from the time of appearance of symptoms, two patients were in the first year of their disease, two in the second year and six in the third year or more. These 10 patients included two with an acute form, two with chronic remissive types and six with a chronic progressive form.

As controls were 10 white men with other neurological diseases, in the same 20 to 40 year age group as the patients with multiple sclerosis; six relatively normal patients were included, as well as four with generalized weakness from debilitating disease processes other than multiple sclerosis.

METHODS

All total body immersions were carried out in an open 5 foot (1.5 M.) bath tub. Changes of bath temperature from 66 to 109 F. were made by the addition of faucet water with constant manual stirring to insure even distribution. The depth of the water was about 14 inches (35 cm.). An ordinary bath thermometer, recording in degrees (F.), was used to determine the bath temperature. Control observations were made at the same time in the empty tub. For the immersion of a single arm at temperatures from 112 to 115 F., a large steel basin was used, water being poured in and emptied off. The immersion of both legs at temperatures from 80 to 110 F. was also performed in the bath tub, with the water rising to the iliac crests.

Certain observations by the patient were recorded with reference to strength, speech, vision and sensation. Tested performances included the measurement of grip strength with a dynamometer and of leg strength by the height of maximum foot elevation. The repetition of standard test phrases determined dysarthria. Visual acuity was measured on the standard Snellen eye chart. The central visual fields were examined, using 1 to 5 mm. white test objects at a distance of 1 meter under constant 100 watt illumination in the darkened bathroom. The measurements of scotomas as recorded were made directly on the black screen during the time the visual fields were examined

As a further investigative technique, tourniquets were applied to the arm during single arm immersion experiments. By way of differentiation, the term "venous tourniquet" indicated a tourniquet on the upper arm blocking venous return from the arm with the radial pulse palpable. By "arterial tourniquet" is designated a blood pressure cuff on the upper arm, inflated to a pressure of 20 to 30 mm. of mercury above the systolic blood pressure, with no pulsations felt over the radial artery.

For dry heating experiments, a standard fever cabinet was used, with cabinet and oral temperatures followed continuously. This method will be described later.

Venous clotting times were measured on blood from a vein of the forearm by the Lee-White method. Serum calcium, serum cholesterol and serum potassium were determined by a large hospital laboratory, using standard procedures.

A description of the method of using a skin temperature machine will be given under that section.

TABLE 1.—*Summary of Data from Total Body Immersion of Six Patients with Multiple Sclerosis and Four Control Patients at Temperatures from 105 to 109 F.*

	Immersion Conditions		Observations					
				Tested Performances				
Patients	Duration, Min.	Temperature, F.	Untested Subject's Report of Weakness	Decrease in Grip Strength		Decrease in Leg Strength	Decrease in Visual Acuity	Increase in Dysarthria
Multiple Sclerosis Group								
A. O.	15	108	Marked	100%	100%	Marked	.....	Anarthria
H. W.	24	108	Marked	40%	50%	.....	None	Marked
H. D.	34	108	Marked	50%	40%	Moderate	None	Moderate
F. L.	20	107	Marked	0%	60%	.....	Slight	Marked
A. A.	8	105	Marked	80%	90%	Moderate	.....	Anarthria
J. W.	20	106	Moderate	0%	0%	Moderate	Marked	Slight
Control Group								
J. F.	33	109	None	0%	0%	None	None	None
W. H.	38	109	Slight	10%	5%	None	None	None
H. H.	33	109	Moderate	10%	0%	None	None	None
E. C.	35	109	Moderate	0%	0%	None	None	None

RESULTS

I. TOTAL BODY IMMERSION EXPERIMENTS

A. The total body immersion (head excluded) of three patients from the multiple sclerosis group for an average time of 18 minutes in cold water (66 to 73 F.) caused moderate discomfort, no pain and slight shivering. Body temperature dropped 0.5 degree (F.), on the average. There was no change in general strength (by the patient's observation) or in the tested observations of arm strength, leg strength, speech, visual acuity, arm reflexes or resistance to passive stretch in the arms.

In hot water (table 1), using six multiple sclerosis patients, the periods of immersion necessary to produce definite changes were for 15, 24, 34, 20, 8 and 20 minutes at 108, 108, 108, 107, 105 and 106 F., respectively. In five patients, extreme generalized weakness ensued; in one, moderate weakness. One subject completely lost voluntary motor power, entering a flaccid state, without changes in blood pressure, respiration or consciousness. Two patients became unable to prevent themselves from sliding completely under water without support. The six patients

all showed increased dysarthria, two becoming able only to mumble, two severely dysarthric and two moderately or slightly so. Grip strength, as measured bilaterally, decreased 100 per cent from control readings (preheating) in one patient, 80 to 90 per cent in one, and 40 to 50 per cent in 2 patients. With one subject there was a unilateral drop of 60 per cent, and with one subject, no change in grip strength. The loss in leg strength was complete in one subject, moderate in three and not recorded in two. While two patients denied change in visual acuity, one observed slight blurring, and the vision of one changed from 20/30 and 20/100 to 20/600 and 20/600. Of the four patients examined, three showed no changes in reflexes or resistance to passive stretch in the arms; in one subject both were slightly increased.

All these changes in function produced with bath heating were immediately reversible on cooling. In three subjects a complete return to control readings occurred from emptying the tub in 12, 7 and 9 minutes. Two patients recovered in tepid water in seven and eight minutes, respectively. One patient, after 51 minutes in hot water at 108 F., suddenly had carpopedal spasms and muscular spasms of the lips and lower part of the face, which responded immediately (in one minute) to an intravenous injection of calcium gluconate.

Associated phenomena in these six patients included a rise of 0.2 to 3.4 degree (F.) in oral temperature, coming concurrently with the weakness, and tachycardia commensurate with elevation of body temperature. A slight drop in systolic pressure and slightly more in diastolic pressure occurred. Tachypnea developed only after prolonged heating.

B. As controls, four relatively intact subjects were used, their hospital diagnoses being atypical facial pain, herniated nucleus pulposus, sciatic pain (left) and peripheral neuropathy of the forearm secondary to trauma.

Immersions were for 33, 38, 33 and 35 minutes, at 109 F., a heating period longer than any required to cause a definite change in the group of multiple sclerosis patients. Two patients reported moderate generalized weakness; one, slight weakness; one, none. There was no dysarthria. Arm strength as measured bilaterally decreased 10 and 5 per cent from the control readings in one patient, 10 and 0 per cent in one patient and not at all in two patients. Leg strength and vision were unaffected. Three of the four complained of slight "dizziness" or "light headedness." There were tachypnea in one and flushing of the face in two patients.

II. Experimental Immersion of Both Lower Extremities

Three patients from the multiple sclerosis group were subjected to the immersion of both lower extremities in cold, tepid and hot water, and the changes in visual and motor symptoms and functions compared with control observations made immediately before in an empty tub.

In cold water at 80 F. for 20 minutes, one patient had slight discomfort from chilliness, but, aside from the patient's observation of slight generalized weakness, no change in arm strength, leg strength, dysarthria or visual acuity occurred. There was a drop of 1.8 degree (F.) in oral temperature. In tepid water, for 20 minutes at 99 F., no change in any of the observed symptoms or functions appeared.

However, hot water produced definite effects. Immersion of three multiple sclerosis patients was for 17, 50 and 28 minutes, at 109, 106 and 110 F., respectively. Two of the three exhibited moderate generalized weakness, decreased grip strength

of 25 to 50 per cent below control readings, moderate decrease in leg strength, moderate increase in dysarthria and a slight decrease in visual acuity (one patient only), all changes being concomitant with an increase of 1 and 1.5 degrees (F.) in body temperature.

The third patient (J. W.) showed only a moderate increase in his dysarthria and a decided loss of visual acuity, no other observations being followed, except repeated examinations of the central visual fields. In these (figs. 1 and 2), the central scotoma in the right eye enlarged from 14 by 13½ inches to 16 by 26 inches (35.5 by 34.3 cm. to 40.6 by 66 cm.) and in the left eye from 2 by 8 inches to 15 by 23 inches (5 by 20 cm. to 38 by 58 cm.). In addition, with leg heating, a separate

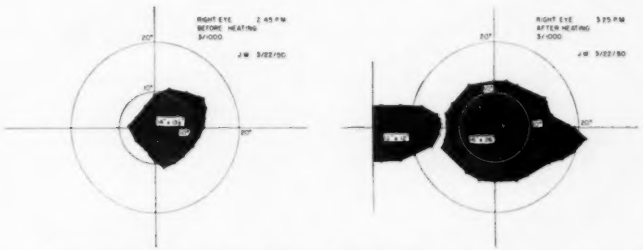

Fig. 1 (J. W.).—Central visual field of right eye examined with a 3 mm. white test object at a distance of 1 meter, before and after leg heating at 110 F.

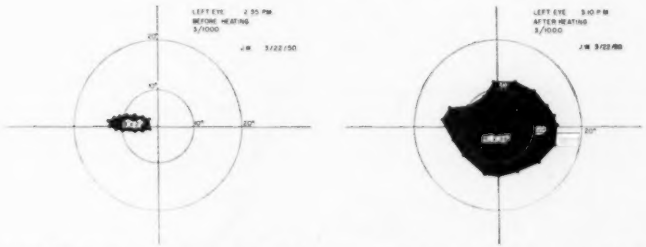

Fig. 2 (J. W.).—Central visual field of left eye examined with a 3 mm. white test object at a distance of 1 meter, before and after leg heating at 110 F.

paracentral scotoma, 12 by 12 inches (30 by 30 cm.), developed in the nasal field of the right eye.

All the changes in visual and motor performance produced by leg heating cleared, on cooling, in 19, 8 and 15 minutes, respectively. Before disappearing with cooling, the same changes in visual fields were recorded in the face of local cooling of the eyes and frontal areas for eight minutes with an ice cap.

III. Experimental Immersion of One or Both Arms in Hot Water

A. The experimental immersion of one arm in hot water (table 2) was done seven times on five patients with multiple sclerosis. Heating periods were for 46, 34, 44, 27, 29, 50 and 42 minutes at 114, 114, 112, 114, 113, 112 and 112 F., respectively. A definite change in visual and motor function occurred in 18, 8, 20,

12, 8, 10 and 5 minutes, respectively. On removal of the arm from the hot bath, complete recovery, including visual field changes, occurred in 12, 10, 21, 7, 14, 7 and 10 minutes.

In considering the four patients in this group on whom the usual observations were made during five heating experiments, severe generalized weakness appeared in all experiments. Arm strength was not affected in one subject but dropped 50 and 25 per cent, 66 and 75 per cent, 0 and 50 per cent, and 50 and 60 per cent below base line determinations in the other four experiments. Moderate leg weakness was seen in three subjects, with no determinations recorded in the other two. Of the four subjects, three showed a marked increase in dysarthria, and one, a moderate increase. In three experiments visual acuity decreased moderately. A mild tachy-

TABLE 2.—*Summary of Data from the Single Arm Immersions of Five Patients with Multiple Sclerosis and Six Control Patients*

	Immersion Conditions			Observations					
					Tested Performances				
Patients	Time, Min.	Temperature, F.	Immersion Period for Definite Reaction to Heat, Min.	Untested Subject's Report of Weakness	Decrease in Grip Strength		Decrease in Leg Strength	Decrease in Visual Acuity	Increase in Dysarthria
Multiple Sclerosis Group									
F. M.	16	114	18 (left) *	Marked	0%	0%	Moderate	None	Moderate
A. O.	34	114	8 (right) *	Marked	50%	25%	.....	None	Marked
A. A.									
a)	44	112	20 (right) *	Marked	66%	75%	Moderate	Moderate	Marked
b)	29	113	8 (left) *	Marked	50%	60%	.....	Moderate	Marked
F. I.									
a)	27	114	12 (left) *	Marked	0%	50%	Moderate	Moderate	Marked
b)	50	112	10 (right) *	Marked	....	....	.....	Moderate †	Moderate
J. T.	42	112	5 (left) *	Moderate	....	....	Marked	Moderate †	Moderate
Control Group									
A. M.	22	115	.. (right) *	None	10%	0%	.....	None	None
W. P.	27	115	.. (right) *	None	0%	0%	.....	None	None
R. S.	24	115	.. (right) *	None	5%	0%	.....	None	None
W. W.	21	115	.. (right) *	None	0%	0%	.....	None	None
A. D.	24	115	.. (right) *	None	0%	0%	.....	None	None
J. G.	21	115	.. (right) *	None	0%	0%	.....	None	None

* Indicates which arm was immersed in hot water.
† Visual fields determined at time of decreased visual acuity.

cardia appeared in two subjects and none in one subject, who, however, had a marked reaction to the heating (weakness). Measurement of the blood pressure revealed a slight drop in diastolic pressure. While body temperature rose 1.1 and 1.0 degrees (F.) in two patients, it remained at 98.4 F. in one and fell 0.2 degree (F.) in another, both of whom manifested definite weakness and increased dysarthria. A reaction of yawning, ptosis and subjective lightheadedness ensued in three subjects. No alteration in reflexes or resistance to passive stretch was seen.

With two multiple sclerosis patients, emphasis was placed on visual field examinations, before and during arm immersion. Both exhibited moderate generalized weakness and dysarthria, so that the usual reaction appeared to be occurring. Coincident with a moderate drop in visual acuity, both subjects showed enlargement of previously present central scotomas. One subject (F. I.) (figs. 3 and 4), in the left eye, maintained a 3 by 4 inch (7.5 by 10 cm.) blindspot, but his central scotoma enlarged from 1½ by 1½ inches (3.8 by 3.8 cm.) to 9½ by 10 inches (24 by 25.4

cm.). A 6½ inch (16.5 cm.) defect appeared separately in the midline superior field. In the right eye, originally, there was a 4 by 4 inch (10 by 10 cm.) central scotoma connected with a 6½ by 8 inch (16.5 by 20.3 cm.) blindspot. On heating, a 21 by 20½ inch (53.3 by 52 cm.) central scotoma enveloped both. For the other patient (J. T.) a 5 by 13 inch (12.7 by 33 cm.) central defect enlarged to 9 by 13½ inches (22.9 by 34.3 cm.). A 17 by 13 inch (43.2 by 33 cm.) central defect in the other eye enlarged to 19 by 15 inches (48.3 to 38.1 cm.). In addition, a defect across the entire superior field also manifested itself. These central field defects were slightly variable, but the most constant defects have been recorded. All changes in the visual fields disappeared immediately on cooling.

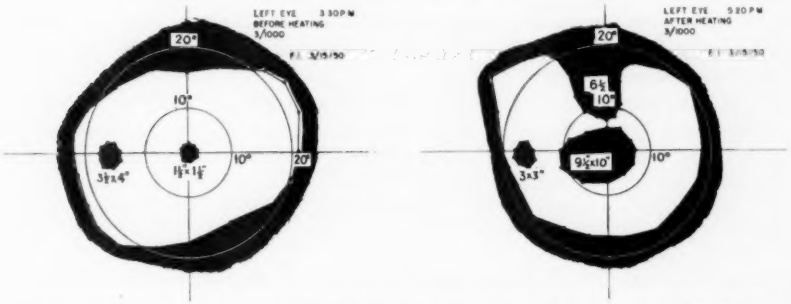

Fig. 3 (F. I.).—Central visual field of left eye examined with a 3 mm. white test object at a distance of 1 meter, before and after single arm immersion at 112 F.

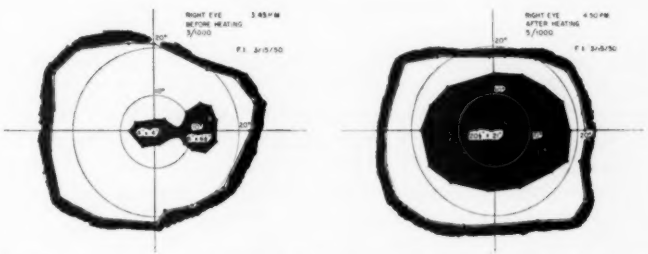

Fig. 4 (F. I.).—Central visual field of right eye examined with a 3 and 5 mm. white test object at a distance of 1 meter, before and after arm immersion at 112 F.

With two subjects, an identical reaction of weakness, dysarthria and decreased visual acuity was produced by separate immersion of the right and the left arm. These results are included above.

One patient, subjected to the heating of one arm for 36 minutes at 113 F. and of both arms for 37 minutes at 114 F., evidenced no changes in general strength, arm strength, leg strength, dysarthria, visual acuity, blood pressure or pulse. His body temperature rose 0.7 F.

Another patient underwent single arm immersion for 30 minutes at 114 F. Slight increase in dysarthria and a complaint (untested) of leg weakness occurred, but generalized weakness, arm strength and visual acuity did not alter. In an additional experimental procedure, with both arms immersed for 45 minutes at 115 F.,

though no other changes occurred, vision dropped from 14/40 and 14/20 to 14/200 and 14/200. No change in ocular muscle or pupillary function was noted. On removal of the arms from the bath, within six minutes, visual acuity returned, stepwise, to preheating levels. With immersion of one arm, body temperature rose 1.0 F.; with immersion of both arms, 2.2 F.

In the selection of a control group, it was decided that a more chronically ill, debilitated patient should be used in an attempt to find out whether this response to heat was present in other chronic illnesses. The six controls included four such patients, with the following diagnoses: paraplegia, secondary to transverse myelitis with infected decubitus ulcers; cerebral laceration, recent; traumatic neuropathy, left posterior tibial nerves, and pneumonitis, probably virus, recent; and syphilis of the central nervous system, dementia paralytica, active. For two relatively normal controls the diagnoses were herniated nucleus pulposus and painful scar of the left posterior part of the thorax.

Single arm immersion of these six control subjects was for 22, 27, 24, 21, 24 and 21 minutes at 115 F. (table 2). In the entire group, two subjects evidenced a 5 to 10 per cent unilateral decrease in arm strength, but there were no other changes in general strength, speech or visual acuity. As an average, there was a 1.6 degree (F.) rise in oral temperature. Mild "lightheadedness" and a slight degree of ptosis occurred, each once.

IV. Experimental Immersion of One Arm in Hot Water, Using A Tourniquet

Eight procedures were carried out on three patients. After a single arm was immersed in hot water and recorded observations compared with base line measurements, the arm was removed, and a short period later, when complete recovery had occurred, immersion of the same arm was repeated, using either a "venous" or an "arterial tourniquet."

Of three patients on whom the venous tourniquet was used, two exhibited the usual reaction of weakness, dysarthria and visual loss, in spite of the venous obstruction on the arm. The reaction, however, seemed of less intensity. The remaining patient, with one arm immersed for 12 minutes at 114 F., evidenced moderate generalized weakness, a 50 per cent decrease in the strength of the nonimmersed arm, moderate decrease in leg strength, pronounced dysarthria, and a decrease in visual acuity from 5/30 and 5/60 to 5/50 and 5/150. After recovery and reimmersion with the venous tourniquet in place for 25 minutes at 114 F., he showed no generalized weakness, a 15 per cent decrease in the strength of the nonimmersed arm only, no decrease in leg strength and no increase in dysarthria. There was a drop in vision from 5/30 and 5/60 to 5/40 and 5/70, but this was less severe than before. Without the tourniquet, body temperature rose 1.0 F.; with it, 0.6 F.

The two patients who had reacted adversely to the arm heating with a venous tourniquet were retested, using an arterial tourniquet. One, who had reacted to eight minutes of a single arm immersion at 114 F. and shown moderate generalized weakness, no change in arm strength, moderate decrease in visual acuity and pronounced dysarthria, differed in his reaction with the arterial tourniquet in place. Under those conditions, when the arm with the tourniquet was immersed for nine minutes at 114 F. he showed no general weakness, no change in arm strength, no decrease in visual acuity and no increase in dysarthria.

The other patient showed, with arm heating alone for 10 minutes at 114 F., pronounced generalized weakness, a 25 per cent decrease in the strength of the nonimmersed arm only, a moderate decrease in visual acuity and severe dysarthria, coincident with a 0.5 degree (F.) rise in body temperature. Arm immersion for 10 minutes at 114 F. with the arterial tourniquet in place produced no general weakness, a 50 per cent reduction in the strength of the arm with the tourniquet, no loss of strength in the nonimmersed arm, no change in visual acuity and no dysarthria. In this instance there was no change in body temperature.

In these testing situations, all three patients reacted adversely to single arm immersion in hot water. In one patient, a venous tourniquet partially prevented the occurrence of the reaction; in two patients an arterial tourniquet was required for complete interference. A considerable amount of pain was caused by the tourniquet when the arm was immersed in hot water. Whether the pain affected testing results cannot be stated. In one instance the arm with the tourniquet became weak when immersed.

V. Evaluation of the Response of Multiple Sclerosis Patients to Fever Cabinet Heating

To learn whether these visuomotor changes from heating would occur in an environment of dry heat, two patients from the multiple sclerosis group were heated in a fever cabinet.

Method.—Base line observations (see above) were made with the patient sitting on a wooden chair inside an open standard fever cabinet. For heating, the cabinet was closed, and the internal temperature slowly elevated to body temperature and then higher. The heating was from electric bulbs. Mouth temperatures and internal cabinet temperatures were closely followed. The cabinet was opened briefly for testing.

Cabinet heating for 19 and 16 minutes, with elevation of the cabinet temperature to 100 F. for 10 minutes, produced in the two patients no changes in general strength, arm strength, speech or vision. In one patient there was slight improvement in visual acuity; in the other, a 15 and 25 per cent increase in arm strength. Body temperature rose 0.8 F. in one and dropped 0.5 F. in the other.

As the cabinet temperature was further elevated, definite changes occurred. Heating for 28 minutes, with one subject, as cabinet temperature rose from 100 to 120 F. and stayed at 115 F. for 20 minutes, produced marked generalized weakness, a unilateral decrease in arm strength of 33 per cent, moderate increase in dysarthria, moderate decrease in visual acuity and a 1.7 degree (F.) rise in oral temperature. As for the other patient, the cabinet temperature was raised from 100 to 115 F. in 14 minutes and maintained at 115 for eight minutes. He evidenced extreme generalized weakness, a 50 and 60 per cent decrease in the strength of both arms, a moderate decrease in visual acuity, marked dysarthria and a 0.1 degree (F.) increase in body temperature. In both patients complete recovery of the tested visuomotor performances in 20 and 18 minutes of cooling occurred. In both patients the type of reaction to the heating in the cabinet was the same as that which each subject showed in a hot bath.

VI. Further Investigative Procedures

A. *Venous Coagulation Time* (Lee and White).—In the six controls subjected to single arm immersion (section III), clotting times were determined

before and during heating. A variation of three increases and three decreases occurred, in the average range of + 0.5 to — 1.5 minute. In six multiple sclerosis patients undergoing single arm immersions (four), immersion of both arms (one) and total body immersions (three), all done while showing a visuomotor reaction to heating and compared with preheating controls, four increases, averaging + 1.8 minutes, and four decreases, averaging — 3.7 minutes, were recorded. Except for indicating a more labile response of the venous clotting time to heating in multiple sclerotic patients, no significant differences were found in the two groups.

B. *Serum Calcium, Cholesterol and Potassium.*—In the same six controls (section III), and in four multiple sclerosis patients, undergoing single arm immersions and evidencing an adverse reaction to heating, no changes were observed in serum cholesterol values determined before and during heating. In both groups changes of ± 0.5 mg. per 100 cc. in the serum calcium occurred, but there was no group difference and no reliable changes from the heating. Serum potassium determinations in one multiple sclerosis patient did not change with heating of one arm.

C. *Direct Observation of the Retinal Vessels.*—In ophthalmoscopic examination of three patients with multiple sclerosis, done before and during a heating reaction, no gross measurable changes were observed in the caliber of the retinal vessels or in the color of the optic disks.

D. *Measurement of Skin Temperature.*—In accordance with the previous experimental observation that in normal persons immersion of one arm or leg in hot water produces vasodilatation and elevation of skin temperature in the other, non-immersed extremities (Landis-Gibbon phenomena), it was decided to compare accurately and frequently body and skin temperatures of the multiple sclerosis patient undergoing partial immersion and to attempt to correlate any variations in these values with the appearance of the described reaction of weakness, dysarthria and visual changes during body heating.

Method: With the patient in an empty bath tub, thermocouple leads from a Speedomax recording skin temperature machine were placed under the tongue and on various parts of the body, as well as being used to record the room temperature. Each of the eight leads recorded three times every two minutes.

Two patients were used. In one patient leg immersion only was carried out, for 43 minutes at 90 to 108 F. A bath temperature of 90 to 100 F. for 19 minutes and of 108 F. for 18 minutes was maintained. With two leads recording the oral temperature and one lead on the skin of each shoulder, no change in strength, visual acuity or body temperature was observed from immersion for 19 minutes at 90 to 100 F. During this period, however, there was a rise of 2.0 degrees (F.) in skin temperature, then a swing back to preheating levels. As heating at 108 F. began, the body temperature rose 1.7 F., with a concomitant rise in skin temperature of 2.0 to 3.0 degrees (F.) on both shoulders. After these changes in temperature had already occurred, visual acuity decreased slightly.

During the last 10 minutes of heating at 108 F., with body temperature remaining approximately the same, skin temperature continued to rise to 3.0 or 4.0 F. above preheating levels. As the last change in skin temperature occurred, the patient's visual acuity decreased more and severe generalized weakness and slight loss of grip strength manifested themselves.

A similar procedure was carried out on the second patient, using one lead on the right shoulder. During immersion of both legs for 11 minutes at 99 F., the body temperature rose 1.0 F., and the skin temperature showed only a 0.5 degree (F.) swing from preheating levels. No changes in strength, speech or vision occurred. Then, as the legs were heated for 14 minutes at 108 F. there was a period of nine minutes during which skin and body temperatures remained level. At this time, a striking decrease in vision from 6/10 and 6/5 to 6/200 and 6/200 had already taken place. During the last five minutes, the body temperature rose 2.0 F. and the skin temperature 4.5 F. Finally, slight dysarthria and moderate leg weakness appeared. The entire procedure on this last patient was repeated after the patient had, 30 minutes before, received 1.2 Gm. of acetylsalicylic acid orally. Immersion was for 14 minutes at 108 F. A reaction identical with that first described occurred.

It was felt that the visuomotor reaction to heating appeared with a corresponding rise in oral and skin temperatures. The rise in skin temperature occurred in non-immersed parts of the body. In one instance, the rise in skin and mouth temperatures preceded the reaction; in the other, it followed.

E. *Chemical Agents.*—Various chemical agents have been used in an attempt to modify this visuomotor reaction to heating. These have included tetraethyl ammonium chloride, acetylsalicylic acid, ergotamine tartrate and nicotinic acid. The results have so far been inconclusive.

COMMENT

The medical investigation of the effects and therapeutic possibilities of hot baths has a long historical sequence. The immersion of the body in hot water has been known since 1909 [6] to elevate body temperature, with a concomitant rise in pulse and respiration rate and a decrease in the carbon dioxide tension of the alveolar air. Various other investigative studies have been carried out to ascertain the changes induced in the human organism by subjecting him to an external environment of hot water. Reported changes include a drop in diastolic blood pressure, diuresis, appearance of palpitations, feelings of pulsations in the vessels of the extremities and the onset, after long heating periods, of irritability and excitement.[7] A detailed review of the physiological responses to heat has been made by Bazett.[8] Additional observed changes in the circulation in response to heating include an increased minute volume of the heart [9] and vasodilatation of the skin with increased skin circulation and elevated skin temperature.[10] In studies of artificial fever induced by a fever cabinet and hot baths, there was with body heating a decided increase in pulse volume in the finger, as recorded by a plethysmograph.[11] These changes

6. Hill, L., and Flack, N.: The Influence of Hot Baths on Pulse Frequency, Blood Pressure, Body Temperature, Breathing Volume and Alveolar Tensions of Man, J. Physiol. **38**:57, 1909.

7. Bazett, H. C.: Studies on the Effects of Baths on Man: I. Relationship Between the Effects Produced and the Temperature of the Bath, Am. J. Physiol. **70**:412, 1924.

8. Bazett, H. C.: Physiological Responses to Heat, Physiol. Rev. **7**:531, 1927.

9. Barcroft, J., and Marshall, E. K.: Note on the Effect of External Temperature on the Circulation in Man, J. Physiol. **58**:145, 1923.

10. Lewis, T.: Studies on Capillary Pulsation, with Special Reference to Vaso-Dilatation in Aortic Regurgitation and Including Observations on the Effects of Heating the Human Skin, Heart **11**:151, 1924.

11. Johnson, C. A.; Osborne, S., and Scupham, G.: Studies of Peripheral Vascular Phenomena: The Effect of Artificial Fever on the Pulse, Volume Changes of the Finger, Am. J. M. Sc. **190**:485, 1935.

have been confirmed, in part, during elevation of body temperature by short wave radiation.[12]

Thus, it has been well substantiated that heating the body in hot water causes generalized vasodilatation, generalized increase in skin temperature, tachycardia and lowered diastolic blood pressure, all changes that would seem to increase blood flow.

As to the effects of hot baths or heating on cerebral circulation, no definite study has been carried out.[7] None of the various methods of studying cerebral blood flow has as yet been used [13] to determine whether the cerebral vessels constrict or dilate or are unresponsive when the body is heated. During heating in hot baths, increased amounts of bromide, as compared with bromide levels for the blood, have been measured in the cerebrospinal fluid, but such evidence is indirect.[14] Autopsies on 17 persons who died of therapeutic hyperpyrexia (one induced by hot baths) have revealed congested cerebral vessels in 13 of 16, with petechiae in 4 of 16,[15] but anoxia and vascular collapse preceding death render invalid the use of such evidence to determine changes in cerebral circulation during heating. A similar result has been obtained in the pathological study of dogs dying in hot baths at a body temperature of 110 F.[16] Here, autopsy studies showed congested, edematous meninges, engorged blood vessels and congested brains, but it is not possible to reach any conclusions from these data. It has been observed by Mehrtens and Allred [17] that, with the use of hot baths to precipitate convulsions in two epileptic patients, while measuring cerebrospinal fluid pressure with a tambour through a subtemporal decompression, heating in a hot bath for 25 to 30 minutes produced a gradual rise in cerebrospinal fluid pressure, with a sudden rise that just preceded a convulsion and seemed to be independent of the rise in blood pressure.

In the experimental work just described, it would seem that, in a group of 10 multiple sclerosis patients, painless total and partial immersion of the body produces a reaction of generalized weakness and testable arm weakness and leg weakness, increase in dysarthria, decrease in visual acuity and changes in visual fields. No changes in sensation or reflexes have as yet appeared during heating. This adverse visuomotor response to heating does not occur after immersion in cold or tepid water and has not been seen in the controls so far tested. These controls have included relatively normal persons and patients with debilitating neurological diseases. The reaction to heating seems to appear with the legs, both arms or one arm immersed in hot water. Either arm, if immersed, will produce a reaction in the subject. When one arm is immersed, the reaction can be interfered with by using an arterial tourniquet on the arm above the level of immersion. It has been possible to reproduce this adverse reaction to heat by using dry heat in a fever cabinet. The reaction occurs usually, but not necessarily, with a slight elevation of body tempera-

12. Bierman, W., and Fishberg, E. H.: Some Physiologic Changes During Hyperpyrexia Induced by Physical Means, J. A. M. A. **103**:1354 (Nov. 3) 1934.

13. Schmidt, C. F.: Personal communication to the author.

14. Mehrtens, H. G., and Pouppirt, P. S.: Effect of Hyperpyrexia, Produced by Baths, on Permeability of the Meninges, Proc. Soc. Exper. Biol. & Med. **26**:287, 1929.

15. Gore, I., and Isaacson, N. H.: The Pathology of Hyperpyrexia: Observations at Autopsy in 17 Cases of Fever Therapy, Am. J. Path. **25**:1029, 1949.

16. Dobin, N. B.; Neymann, C. A., and Osborne, S. L.: Pathologic Changes in the Central Nervous System Resulting from Experimentally Produced Hyperpyrexia, J. Neuropath. & Exper. Neurol. **8**:295, 1949.

17. Mehrtens, H. G., and Allred, W. L.: Effect of Hyperpyrexia Produced by Baths upon the Intracranial Pressure in Epileptics, Proc. Soc. Exper. Biol. & Med. **28**:604, 1931.

ture. It is also associated with an elevation of skin temperature in nonimmersed parts of the body, but the reaction to heating and changes in skin and oral temperatures are not concurrent. The reaction to heating does not depend on the clinical type or the duration of the disease. Each patient has his own particular response pattern to heat, which different methods of heating bring out. No light has been shed on the mechanism of this response to heating by studies of venous coagulation time, and serum calcium and potassium and cholesterol levels. During heating no changes have been observed in the caliber of the retinal vessels. Attempts to block this reaction with acetylsalicylic acid, caffeine and ergotamine tartrate have failed.

In the past, in an attempt by physicians to discover effective therapeutic approaches to multiple sclerosis, patients have been subjected to various forms of heating. On the rationale that the disease may be caused by a virus and that a heat-sensitive organism may be found in the spinal fluid,[18] 12 patients were subjected to immersion in a hot bath at 110 F. for 10 minutes.[19] During these periods of elevation of body temperature to 108 F., restlessness and confusion, followed by "a period of mental depression," were noted. After 115 baths were given to 12 patients, the condition of four showed improvement; that of six showed no change, and that of two became worse. No description of changes in the neurological examination during the period of elevation of body temperature was made. In a general discussion of therapy with hot baths,[20] with reference to multiple sclerosis, the observation was made that "muscle weakness ordinarily was not favorably influenced."

Several attempts have been made to treat multiple sclerosis with electropyrexia. With local diathermy, given over the spinal cord, to 13 patients, 10 showed improvement; one relapsed and was then cured; one became worse, and one had questionable results,[21] but the criteria for improvement are vague, and no control series is reported. In a discussion of 25 patients with multiple sclerosis treated with electropyrexia,[22] with elevation of body temperature to 103 or 105 F. for eight to 10 hour periods, 44 per cent were much improved and an additional 40 per cent were less improved. There were two deaths. No good criterion of improvement was employed, and there was no report of the patient's neurological status during heating. In another report, in 1931, on the value of diathermy in this disease,[23] one patient with multiple sclerosis improved, and "results have far exceeded our expectations."

Interesting and pertinent observations have been made in the treatment of multiple sclerosis with nonspecific protein therapy.[24]

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18. Chevassut, K.: The Etiology of Disseminated Sclerosis, Lancet **1**:552, 1930.

19. Lindemulder, F. G.: The Therapeutic Value of High Temperature Baths in Multiple Sclerosis, J. Nerv. & Ment. Dis. **72**:154, 1930.

20. Mehrtens, H. G., and Pouppirt, P. S.: Hyperpyrexia Produced by Baths: Its Effect on Certain Diseases of the Nervous System, Arch. Neurol. & Psychiat. **22**:700 (Oct.) 1929.

21. Stephenson, J. W.: Diathermy in the Treatment of Multiple Sclerosis, Physical Therap. **44**:336, 1926; Further Observations in the Treatment of Multiple Sclerosis, ibid. **45**:165, 1927; Diathermy in Multiple Sclerosis: Report of Progress, ibid. **46**:373, 1928.

22. Neymann, C. A., and Osborne, S. L.: The Treatment of Some Multiple Scleroses by Electropyrexia, J. Nerv. & Ment. Dis. **79**:423, 1934.

23. Schmidt, W. H., and Weiss, B. P.: Fever Produced by Diathermy: Its Value in Multiple Sclerosis and Other Chronic Disease, Physical Therap. **49**:336, 1931.

24. Young, G. A., and Bennett, A. E.: Non-Specific Protein (Typhoid Vaccine) Therapy of Disseminated Sclerosis: Preliminary Report of Results in 8 Cases, Nebraska M. J. **12**:401, 1927.

After the first intravenous injection, fever of 102 F. results, and the patient had transient blindness and exacerbation of her symptoms. . . . [In another case,] with the second intravenous injection of vaccine, a severe febrile reaction developed and for a few hours the patient had paresthesiae from the waist down and was unable to use her limbs. [In still another case,] at one time, a temperature of 105 F. developed after the injection. The amblyopia became more intense; at times, the patient could not recognize such objects as a knife at 24 inches. Within 48 hours after the injections, the vision would return to normal. . . . The immediate reaction exacerbates the existing symptoms, probably from acute transient edema of the patches of sclerosis.

In general reference to electropyrexia, the comment has been made that fever may bring out latent neurological abnormalities.[25] Interestingly, the case used to illustrate this concept was one of multiple sclerosis, and during fever treatments, while the patient was febrile, there developed paresthesias, dysesthesias, pronounced generalized weakness, hand and foot paralyses and areas of anesthesia, with complete recovery soon after the body temperature returned to normal.

In general, while hot baths, diathermy, fever cabinets and pyrexia induced with foreign protein have been tried several times in the treatment of multiple sclerosis, inconclusive results have gradually led to their disrepute as effective agents. Only rarely has emphasis been placed on the immediate changes in the patient during fever, and clinical data on this point have been scarce. What little evidence there is, however, seems to support the present experimental data and to indicate that heating worsens symptoms in these patients.

Of the changes that seem to appear during heating, the generalized weakness, arm weakness, leg weakness and dysarthria have, in general but not always, been present in the patients with multiple sclerosis before heating. The effect of the hot baths seems mainly to have been one of rendering these dysfunctions more evident. The changes induced by heating that are new, or at least subclinical, have been chiefly decreased visual acuity and changes in visual fields. In a fluctuating disease, such as multiple sclerosis, what is "present," "not present" or "latent" often defies differentiation. Thus, it is at present impossible to know whether heating merely brings out underlying defects in the central nervous system or whether it creates new defects. Perhaps this problem can be elucidated by carrying out immersion experiments on patients with neurological defects from other pathological processes and observing whether heat makes their dysfunctions more obvious.

It has been well established that in normal persons the immersion of one arm causes a rise in skin temperature, i. e., vasodilatation, in nonimmersed extremities (Landis-Gibbon phenomenon), a reaction that is probably blockable with a tourniquet.[26] This effect does not appear in sympathectomized patients, and there is felt to be reflex vasodilatation in the muscles of nonimmersed extremities.[27] It seems

25. Collins, R. T.: Transitory Neurological Changes During Hyperthermia, Bull. Neurol. Inst. New York **7**:291, 1938.

26. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**:1019, 1932. Goetz, R. H., and Ames, F.: Reflex Vasodilatation by Body Heating in Diagnosis of Peripheral Vascular Disorders, Arch. Int. Med. **84**:396 (Sept.) 1949.

27. Barcroft, H.; Bonnar, W. M., and Edholm, O. G.: Reflex Vasodilatation in Human Skeletal Muscle in Response to Heating the Body, J. Physiol. **106**:271, 1947.

not to be correlated with changes in rectal temperature.[28] It is speculated that, in this reflex vasodilatation, vascular changes may come either from warmed blood or from some unknown chemical released in the arm. The phenomenon appears to be a humoral, then a neural, reflex. In the present experiment on patients with multiple sclerosis, during single arm immersion, the elevation of skin temperature in nonimmersed areas is apparently what in normal subjects is called the Landis-Gibbon phenomenon. It is during the period when this phenomenon is in operation that the changes in the patient's neurological status occur. The time relationships, however, are not overlapping. Whether investigation of the present problem with this in mind might be profitable cannot be stated at present.

This reaction to heating in cases of multiple sclerosis should be regarded as an interesting clinical phenomenon. The questions that arise because of it are many and interesting. Although the control groups so far tested have shown no such changes with heating, it is possible that heat will produce similar changes in other patients with diseases of the central nervous system. As cerebral circulation is probably affected by heating, the mechanism by which this occurs and the nature of the response of the cerebral vessels are worthy of investigation. There is also a possible connection between the heating response and the geographical occurrence of multiple sclerosis, its symptomatology and its etiology. As a matter of clinical interest, it has been felt to be worthy of being reported.

CONCLUSIONS

1. A reaction of generalized weakness, testable arm weakness and leg weakness, increased dysarthria, decreased visual acuity and changes in visual fields occurs in patients with multiple sclerosis as a response to total and partial body heating.

2. A similar response to heating has not appeared in the control groups so far tested.

3. An identical reaction appears when patients with multiple sclerosis are heated in a fever cabinet.

4. An arterial tourniquet blocks the reaction when it occurs from the immersion of one arm in hot water.

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28. Martinez, C., and Visscher, M. B.: Some Observations on General Skin Temperature Responses to Local Heating of Human Subjects in a Cold Environment, Am. J. Physiol. **144**:724, 1945.

TREMOR IN PARKINSON'S DISEASE AND ITS INHIBITION BY AMYL NITRITE

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THE BASAL ganglia and the substantia nigra are now generally accepted as the chief sites of pathological changes in the parkinsonian states (paralysis agitans; postencephalitic and arteriosclerotic parkinsonism). It has been suggested that these changes remove or interfere with an inhibitory function of these parts, the characteristic tremor originating elsewhere or representing the pyramidal system functioning without extrapyramidal constraint.

A 6 per second rhythm, known as the theta rhythm, can be recorded from the cerebral cortex. It is believed that this is "paced" by basal ganglia mechanisms. On a few occasions this theta rhythm has been inhibited by the inhalation of amyl nitrite.[1] It appeared worth while, therefore, to try the effects of such inhalations on the tremors characteristic of diseases of the basal ganglia, even though abnormal electroencephalograms have been found to occur only in those cases of post-encephalitic parkinsonism in which personality changes, and not tremor, were present.[1]

This paper gives the results of observations on the effects of amyl nitrite and some other vasodilating drugs, namely, sodium nitrite, glyceryl trinitrate (nitroglycerin), octyl nitrite, histamine and nicotinic acid. By testing a variety of vasodilator drugs, it was hoped to show how far the action of the amyl nitrite depended on this property. A discussion of the pathogenesis of tremor and rigidity, with possible modes of action of amyl nitrite, concludes the paper.

METHODS

Patients with all forms of the parkinsonian state were investigated except those with advanced arteriosclerosis, who readily become syncopal when given vasodilating drugs.

Tremor was recorded by surface electrodes strapped to a forearm, as in electrocardiography. The impulses were fed through the circuits of an electroencephalogram to give a continuous record by means of ink writers. A few records were made by a mechanical system.

Amyl nitrite was inhaled from a capsule crushed into a piece of gauze held close to the subject's nose and mouth. Inhalations were continued until an effect on the tremor became obvious or until unpleasantness from the drug resulted.

The patient always lay quietly on an examination couch, and the nature of the test had been explained to him. No investigation was commenced unless the patient appeared calm and free from apprehension.

Owing to the rapidity and fleeting nature of the effects produced by amyl nitrite, it was often difficult to make rapid and repeated estimations of changes in the blood pressure; for this reason only systolic readings were taken when fluctuations were believed to be rapid.

From the Department of Neurology, King's College Hospital.

1. Hill, D.: Personal communication to the author.

It was not possible to estimate the amount of the amyl nitrite which the patient actually inhaled, and there is no doubt that this quantity varied considerably from patient to patient and one occasion to another; such a variation is inherent in the method of inhalation used and should be allowed for when one is assessing the variability seen in the results.

In certain experiments simultaneous electroencephalographic tracings were taken, and also a lead I electrocardiogram as a record of the pulse rate.

In all cases standard skin electrodes were used, strapped firmly to the selected area, and contact was insured by use of Cambridge electrode jelly.

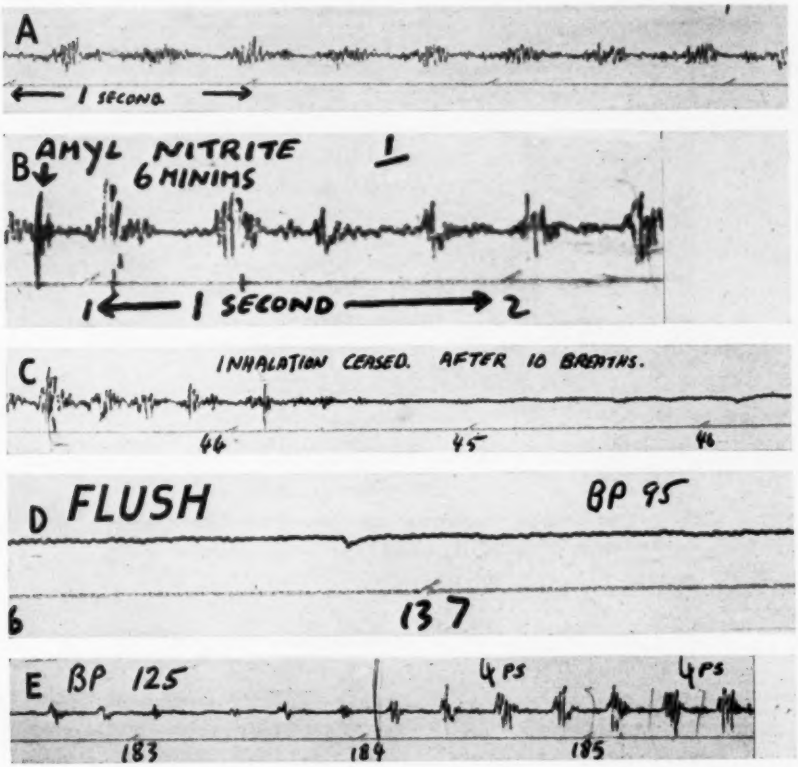

Fig. 1 (case 1).—*A*, tremor tracing; *B*, tremor at commencement of inhalation of amyl nitrite; *C*, cessation of tremor and early part of quiescent phase; *D*, record taken about 1½ minutes after tracing in *C*, showing continued absence of tremor as flush spreads over the face and systolic blood pressure is rising to over 100 mm. of mercury; *E*, return of tremor after about 2½ minutes.

RESULTS

Case 1.—Miss S., aged 57, presented typical postencephalitic parkinsonism, which had had a gradual onset about 24 years previously, following an attack of encephalitis. There was well marked tremor of both arms with extrapyramidal rigidity. These changes were less pronounced in the legs. The blood pressure was 145/100, and the cardiovascular and other systems were normal. In figure 1 *A* is shown a sample of the type of tremor tracing obtained on frequent occasions from this patient. The rate of tremor in this instance was approximately 2.6 per second, with practically no variation.

In *B* (fig. 1) the effect of amyl nitrite on the tremor is shown. At the point indicated, 6 minims (0.36 cc.) of amyl nitrite was inhaled from capsules in the usual way. Before inhalation was begun, the systolic blood pressure was 118 mm. of mercury and the tremor rate was 4 per second. At the normal rate of respiration, 10 inhalations of the drug were taken in 44 seconds, at which point further inhalation was stopped, as the tremor had ceased (fig. 1 *C*). The systolic blood pressure had fallen to 60 mm. at 39 seconds but had risen to 65 mm. at 55 seconds. It remained near this level until 104 seconds, when a slow rise set in, first to 75 mm.,

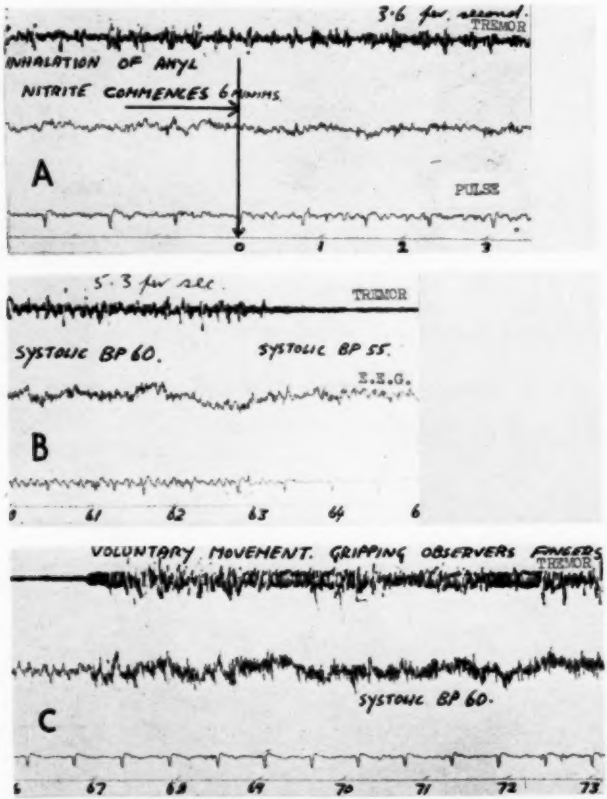

Fig. 2 (case 1).—*A*, simultaneous recording of tremor, electroencephalogram and pulse rate (lead I electrocardiogram) at commencement of experiment; *B*, increasing tremor rate and commencement of quiescent phase; *C*, record taken a few seconds after *B*, showing preservation of full voluntary power.

and reaching 90 mm. at 121 seconds. At 125 seconds a well marked flush spread over the face (fig. 1 *D*). The blood pressure continued to rise, reaching 105 mm. at 143 seconds. As can be seen, tremor remained in abeyance. At 162 seconds the systolic blood pressure was 120 mm. of mercury. At this point the first signs of the impending return of the tremor were visible in the record as a faint and transient fluctuation, lasting nearly three seconds. Up to this point the tremor had been in abeyance two minutes. The blood pressure continued to rise, reaching 130 mm., and the flush disappeared after lasting 46 seconds. At 181 seconds signs of the returning

tremor were evident, and the tremor became well established within the next three seconds, at a rate of 4 per second (fig. 1*E*).

At no time during the experiment did the patient show any signs or symptoms of faintness or discomfort; she lay quietly on a couch with the head and shoulders raised to an angle of 45 degrees. An electroencephalogram taken simultaneously throughout the experiment showed no changes that could be interpreted as due to cerebral anoxemia. The fine vibrations of 50 per second in the electroencephalogram are due to the interference of alternating current mains.

Figure 2*A* again illustrates the effect on Miss S. of the inhalation of 6 minims of amyl nitrite, but on this occasion simultaneous records of the pulse rate (by means of a lead I electrocardiogram) and electroencephalographic and blood pressure readings were also taken. The preinhalation tremor rate was 2.75 to 3.6 per second. Inhalation was then commenced, and, as can be seen, the tremor rate increased to 5.4 per second at 57 seconds, after 12 inhalations (fig. 2*B*). The blood pressure had then fallen from 120 to 70 mm. of mercury. At 63 seconds,

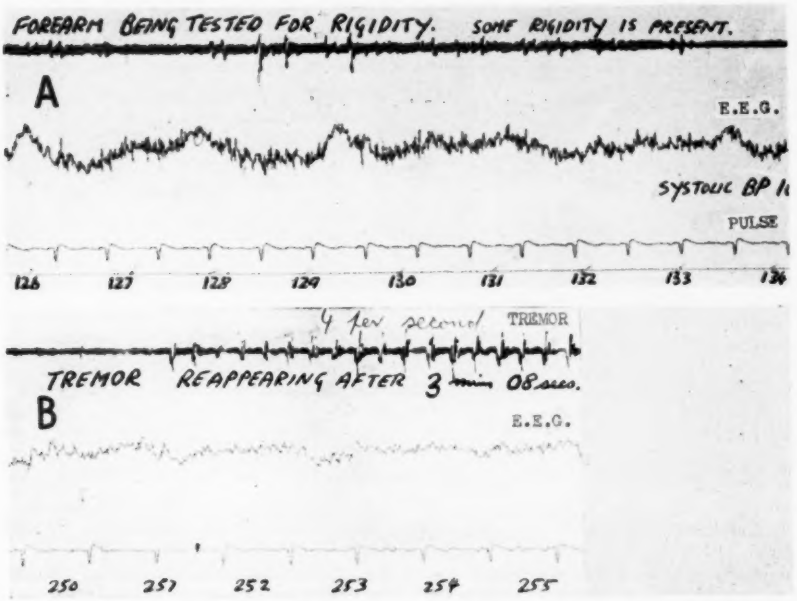

Fig. 3 (case 1).—*A*, tracing taken later than that in figure 2*C*, showing test for rigidity being carried out; *B*, reappearance of tremor.

when the blood pressure was 60 mm., the tremor ceased (fig. 2*B*) and remained in complete abeyance three minutes eight seconds; during this time the ability to carry out voluntary movements, such as gripping the observer's hand, was demonstrated (fig. 2*C*). At 70 seconds the blood pressure had commenced to rise, reaching 90 mm. at 102 seconds, when the pulse rate was 108; at this point a flush appeared over the face. The state of the muscular tone was tested, and extrapyramidal rigidity was found to be still present, though of diminished degree (fig. 3*A*). At 134 seconds the blood pressure was 105 mm. of mercury, and from 125 seconds on was over 125 mm. Tremor, however, did not return until 251 seconds, when it did so at a rate of 4 per second (fig. 3*B*).

In an attempt to exclude any part played by emotions or hyperventilation in the causation of the inhibitions, a record was taken during a conversation with Miss S. in which it was suggested to her that she submit to the inhalation of a "gas." It was believed that this request would cause a certain amount of apprehension until the full nature of the forthcoming test

with carbon dioxide-oxygen mixture (Carbogen) was later explained. However, the frequency of the tremor was not significantly altered. The amplitude was perhaps slightly increased.

The effect of voluntary hyperventilation for a full three minutes was then determined. Simultaneous tremor records and electroencephalograms were made. The prehyperventilation tremor rate was 3 to 4 per second; as a result of hyperventilation the rate increased to an erratic maximum of 8 to 11 per second. At the end of the three minute period of hyperventilation the frequency at once dropped to 6 or 7 per second, and in another 30 seconds it was 4 per second. The electroencephalogram showed no significant change throughout. It thus appears that hyperventilation may increase the rate of tremor. It is open to question, however, whether a patient with extrapyramidal disease can hyperventilate adequately. This subject was capable of prolonged attempts at hyperventilation, with no ill effects.

To assess the significance of vasodilatation and fall in blood pressure in the inhibition of tremor by amyl nitrite, these factors were produced by other means. Thus, the effect of an intravenous injection of 60 mg. of nicotinic acid was tried. Simultaneous recordings of the tremor, the electroencephalogram and the pulse (lead I electrocardiogram) were made. The initial tremor rate was 3.6 to 4 per second, and the systolic blood pressure, 120 to 130 mm.

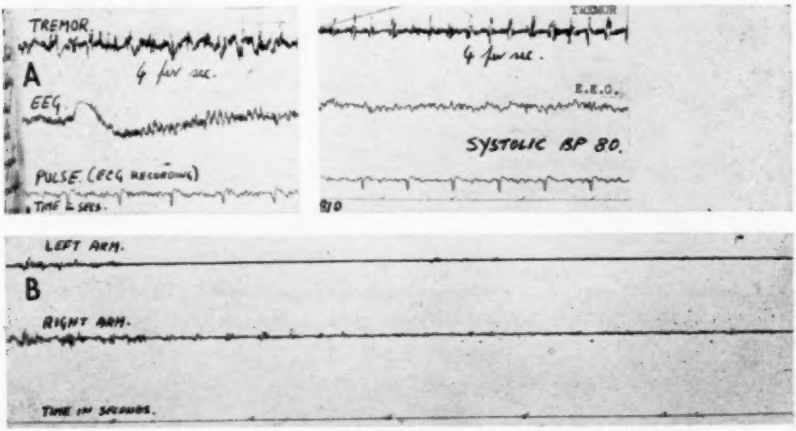

Fig. 4 (case 1).—*A*, failure of nicotinic acid to inhibit tremor in spite of reduction of systolic blood pressure to 80 mm. of mercury; *B*, spontaneous cessation of tremor.

of mercury. At the end of two minutes the rate had increased to 8.2 per second, and the pulse rate was 84. By six minutes 40 seconds the blood pressure had dropped to 98 mm., the tremor rate being 7.2 per second and the pulse rate 96 per minute. The systolic blood pressure dropped slowly over the ensuing minutes, reaching 80 mm. of mercury at the end of 12 minutes, at which time the tremor was 5.2 per second and the pulse rate 72 per minute. From this it appears that, as compared with the duration of the fall in pressure following inhalation of amyl nitrite, the prolonged fall of the systolic blood pressure to a figure well below 100 mm. and the consequent vasodilatation did not materially influence the tremor of the patient on this occasion (fig. 4 *A*). The decrease in amplitude and apparent cessation of tremor, the latter not exceeding two seconds, are no more than that which took place spontaneously and are in contrast to the more prolonged absence of tremor following the inhalation of amyl nitrite. In the case of the latter drug the disappearance of the tremor was noted up to four minutes, during most of which time the systolic blood pressure exceeded 115 mm. of mercury.

To show that the apparent effects of amyl nitrite were not due to spontaneous remissions in the tremor, records were taken simultaneously from both arms on a day when the tremor was unusually quiet and was frequently exhibiting spontaneous cessation, the latter, however, never lasting more than a few seconds (fig. 4 *B*).

CASE 2.—Mr. L., with a diagnosis of postencephalitic parkinsonism, submitted to the inhalation of 3 minims (0.18 cc.) of amyl nitrite on July 31, 1946. The recording of the tremor was by means of a mechanical system in which an index finger was fixed to the surface of a rubber tambour, connected by thick-walled pressure tubing to a second, and smaller, tambour. To the surface of the latter was fixed a light weight lever carrying an ink writer. The rate of the tremor prior to the inhalation varied from 3 to 7 per second. Amyl nitrite was then inhaled, and 18 seconds later cessation of the tremor occurred for 10 seconds; this was followed by recurring periods of cessation, interspersed with short periods of tremor, the longest period of quiescence being 30 seconds. The rate of tremor was not appreciably changed (fig. 5).

CASE 3.—Mr. T., with postencephalitic parkinsonism, on Oct. 8, 1946 inhaled 3 minims of amyl nitrite. It was not until 42 seconds later that any effect was seen, when complete muscular relaxation and cessation of the tremor occurred for periods ranging from three to thirteen seconds.

CASE 4.—Mrs. Nellie S., aged 48, with paralysis agitans of about six years' standing, had constant tremor of both upper limbs, with no periods of spontaneous remission in her waking hours. Inhalations of 6 minims of amyl nitrate caused the blood pressure to drop within 40

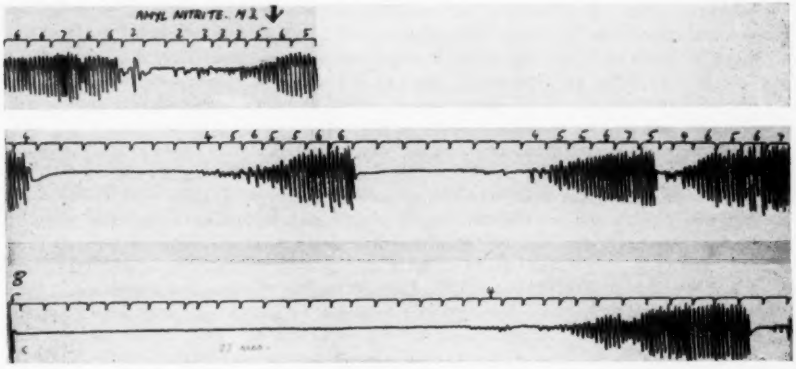

Fig. 5 (case 2).—Effects of amyl nitrite inhalations, shown with a recording mechanical system.

seconds from 110/80 to 90/50; shortly after, a flush spread over the face; by the end of 50 seconds the blood pressure had risen to 130/90, but tremor then ceased completely in both upper limbs for a little over one minute. There was no loss of consciousness or other unpleasant effect.

OTHER VASODILATORS

An attempt was next made to determine whether other drugs in the nitrite series would produce similar, and, if possible, more prolonged, effects; most of the observations were made on Miss S (case 1).

Octyl Nitrite.—Repeated and prolonged inhalations of the drug by means of a nasal inhaler, of a pattern similar to that of a benzedrine® inhaler, produced no change in either the tremor or the blood pressure.

Glyceryl Trinitrate.—Tablets containing up to 0.03 grain (1.9 mg.) were allowed to dissolve slowly on the tongue. By this means the blood pressure was reduced from 110/70 to 95/70, but the only effect on the tremor was a slight, but not significant, decrease. On one occasion when 0.03 grain of glyceryl trinitrate failed to inhibit the tremor, inhalation of 3 minims of amyl nitrite caused the usual cessation of the tremor, on this occasion for three minutes, the blood pressure not falling below 130/80 and the pulse rate not exceeding 84.

Histamine Hydrochloride.—The intravenous injection of 0.1 mg., which produced a well marked flush of the face and a throbbing headache, failed to influence the tremor. The blood pressure dropped to 108/68 during the period of observation.

Sodium Nitrite.—Three grains (0.195 Gm.) was given when the blood pressure was 135/80 and the pulse rate 96, tremor being present as usual. In 11 minutes the blood pressure had fallen to 95/60, and the tremor in the left hand ceased for 20 seconds only. At the end of 27 minutes the blood pressure was 90/60 and the pulse rate 84. Though the tremor was decreased in amplitude very considerably, it was never completely in abeyance. In another six minutes the blood pressure had reached 100/60 and the tremor had fully returned. The patient stated that subjectively there was a definite decrease in the tremor, similar to that which she experienced if she was almost asleep, but that on this occasion it lasted for a much longer time. No unpleasant side effect from the sodium nitrite was noticed. On another occasion 5 grains (0.325 Gm.) of sodium nitrite was given, reenforced by 4 grains (0.26 Gm.) 20 minutes later. Practically identical results were obtained, though the blood pressure did not fall below 90/60 and the pulse rate did not exceed 96.

Another series of observations with sodium nitrite were made on another patient (case 5), a woman of 70 with idiopathic parkinsonism. In one experiment she was given 5 grains of sodium nitrite; at 2:12 p. m. the blood pressure was 175/100 and the pulse rate 75. At 2:18 p. m. the blood pressure was 120/80 and the pulse rate 95. At 2:22 p. m. the blood pressure was 95/65 and the pulse rate 108; the tremor, however, remained unaltered. At 2:26 p. m. the blood pressure was 60/50 and the pulse rate 108, and at 2:28 p. m. the blood pressure sank to 55/45 and the pulse rate was 95. At this point signs of circulatory failure were becoming pronounced: the skin was cold, and the mucosae showed a gray cyanosis; yawning, slurred speech and some confusion were present; the tremor, however, was unaltered. As the systolic blood pressure reached 50 mm., 3 minims of 1:1,000 solution of epinephrine hydrochloride was given intravenously, and continuous oxygen was administered by means of a B.L.B. mask. The blood pressure rose within a few seconds to 160 or 170 systolic, and the patient vomited. At 2:34 p. m. the blood pressure was steady at 110/90. Ephedrine, ½ grain (0.032 Gm.), was given at 2:44 p. m., as the blood pressure had again shown a drop to 90/60. Thereafter it rose slowly but satisfactorily and at 3:40 p. m. was 150/85. Thus, in spite of the fact that 5 grains of sodium nitrite was sufficient to lower the blood pressure to such a level as to cause considerable cerebral anoxemia, the rhythmic tremor was not influenced throughout the period of observation. This patient on other occasions responded to the inhalation of 3 minims of amyl nitrite by the cessation of her tremor for three minutes, the blood pressure not falling below 170/90. Normally this patient's tremor did not cease spontaneously for more than half a minute, and voluntary inhibition was possible for only 20 seconds.

COMMENT

In his classic studies, Kinnier Wilson[2] (1914 and 1925) drew attention to the basal ganglia and brought the light of clinical and experimental research to illuminate much that had been previously in the shadows. As often occurs, however, the more penetrating the light, the further its beams project, enlarging thus the horizon, and so the problem which confronts us. It is unfortunate that in certain respects the conclusions reached by Kinnier Wilson have themselves proved obstacles to further advances.

As a result of experiments on 25 monkeys, Kinnier Wilson[2a] concluded that the corpus striatum was completely autonomous and that there were no fiber connections between it and the cortex, though he was well aware of Marinesco's findings on this point (Marinesco,[3] 1895). It was only in later years that he began

2. Wilson, S. A. K.: (*a*) Brain **36**:427, 1914; (*b*) Lancet **2**:24, 1925.

3. Marinesco, G.: Compt. rend. Soc. de biol. **2**:77, 1895.

to modify this view.[4] It remained for Levin [5] (1936) to demonstrate beyond refutation the existence of such a connection, though Mettler [6] (1942) points out that connections between prefrontal cortex and the caudate nucleus were described in 1893 by Muratoff and by Koeillilers. In Kinnier Wilson's opinion, the corpus striatum is a motor center, though he was careful to state that because its main connections were efferent it did not follow that its function was even similar to that of the corticospinal system. His own view was that it exerted a steadying influence on the pyramidal tracts via the lenticulorubrospinal projections system, and that in some way it was concerned with the maintenance of "tone" in the skeletal muscles. Moreover, the removal or cessation of this steadying influence on the final common path would result in a tremor, which would tend to increase as pyramidal activity increased and so result in an action tremor. This view was echoed with minor variations by Walshe [7] in his Oliver Sharpey lecture for 1929, when he reached the provisional conclusion "that tremor is not a new phenomenon representing a mode of innervation peculiar to paralysis agitans, but is the emergence of a normal cortical rhythm through defect of lower level mechanisms."

Following on the development of new technics during the 1930's, much new information on the anatomy and physiology of these areas has been obtained. Levin [5] showed that the substantia nigra receives fibers from several distinct cytoarchitectural areas of the frontal lobe, chiefly from areas 4 and 6, but also from area 8, and as a result he concluded that the substantia nigra is essentially a motor nucleus, under the direct influence of the neopallium. Less convincing was the evidence for a fiber connection between the cortex and the globus pallidus. Glees [8] (1944) found that in the cat brain the suppressor bands 2s, 3s and 8s are connected with the caudate nucleus by nonmyelinated fibers which arise as collaterals from corticofugal fibers; these collaterals ramify among the cells of the caudate nucleus and enter into the formation of pericellular plexuses. This connection between the strip areas, which are known to be suppressive, and the caudate nucleus can be looked on as supplying an anatomically possible basis for the results obtained by Mettler [9] (1939). In a paper on the connection of the red nucleus, Papez and Stotler [10] (1940) stated the belief that there exists what they termed a "belt line" circuit, by means of which impulses from the pallidum generate a two way circuit between the ventral lateral nucleus of the thalamus and the premotor cortex, at the same time as they excite the function of the red nucleus. Thus, any voluntary activity in the cortex would set into operation simultaneously impulses along the corticospinal tracts and along a cortico-ponto-cerebello-dento-rubro-thalamocortical circuit. These authors believe that such a "reciprocating" mechanism between the cortex, the corpus striatum and the cerebellar cortex facilitates recipro-

4. Wilson, S. A. K.: Modern Problems in Neurology, New York, William Wood & Company, 1928, p. 135.

5. Levin, P. N.: J. Comp. Neurol. **63**:369, 1936.

6. Mettler, F. A.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:162 and 197, 1942.

7. Walshe, F. M. R.: Lancet **1**:963 and 1024, 1929.

8. Glees, P.: J. Anat. **78**:47, 1944.

9. Mettler, F. A.; Ades, H. W.; Lipman, E., and Culler, E. A.: Extrapyramidal System: Experimental Demonstration of Function, Arch. Neurol. & Psychiat. **41**:984 (May) 1939.

10. Papez, J. W., and Stotler, W. A.: Connections of Red Nucleus, Arch. Neurol. & Psychiat. **44**:776 (Oct.) 1940.

cal innervations of the neuromuscular apparatus and hence of smoothness and fine coordinations of muscle action, though Wiener[11] (1949) would see in such a mechanism a good arrangement for automatic control.

Mettler and associates,[9] who studied the effects of electrical stimulation of the corpus striatum carried out against a background of cortically induced movement, found that stimulation of the caudate nucleus, putamen or claustrum inhibited the cortically induced movement and that the effect was most marked on movements initiated in the ipsilateral cortex. Similar stimulation of the globus pallidus caused such a movement to cease uncompleted, the limb being held then in a state of "plastic tonus." Stimulating the substantia nigra in cats and monkeys, these observers found that the tone of the antigravity postural muscles was increased. It is tempting to see a connection between this result of stimulation of the substantia nigra and a possible relation of its destruction in Parkinson's disease to the typical attitude of flexion, one of the constant and outstanding features of the disease.

Reconciliation of the results of Liddell and Phillips[12] (1940) and those of Mettler is possible when it is realized that the former investigators were destroying and the latter were stimulating the substantia nigra. The former obtained increased tone in ipsilateral flexors. The latter on stimulation obtained increased tone in extensors.

Mettler,[6] as a result of experimental investigations of striatal inhibitions by means of lesions placed in the caudate nucleus, putamen or claustrum of cats, the exact position of such lesions being verified subsequently, concluded that while the greatest influence of the parts was exerted on the contralateral side, this was by no means entirely so. They interpreted their evidence as indicating that the function of the corpus striatum is inhibitory. They felt justified in concluding that the caudate nucleus is under some degree of cortical control, which serves to inhibit bodily movement, and, on the contrary, that at least some of the inhibitory power of the cortex is exerted through and by means of the caudate nucleus. Since removal of the frontal cortex, either entirely or in part, does not produce the pronounced signs of release which follow neostriatal injury, the thalamus, which is the only other source of fibers passing into the caudate nucleus, must be considered more important in the ordinary physiology of the neostriatum than the cortex. This inference, however, does not necessarily follow, as it supposes the caudate nucleus to be a site of origin of impulses resulting in muscular activity, a supposition at variance with experimental facts. Moreover, it is by no means certain that there exists in man the same relative importance between thalamus and cortex with regard to their influence over the caudate nucleus as exists in the cat. It may be that as the frontal cortex has developed in man, so, too, has its influence over the caudate nucleus.

If, then, destruction of the corpus striatum removes an inhibitory mechanism which exists between the motor cortex and the anterior horn cell, it would be in agreement with the conclusions reached by Hoefer[13] (1942) as a result of his myographic studies. Hoefer found that in parkinsonian rigidity there is a resting basic muscle activity which is of central origin. This is unlike the state of resting

11. Wiener, N.: Cybernetics, New York, John Wiley & Sons, Inc., 1949.

12. Liddell, E. G. T., and Phillips, C. G.: Brain **63**:264, 1940.

13. Hoefer, P. F. A.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:524, 1942.

spastic muscle, which is electromyographically quiet. The paradox of both powerful volitional activity and section of the pyramidal tracts causing cessation of tremor is at first difficult of explanation, unless it is that both voluntary and "pathological" (meaning those impulses whose arrival at the periphery initiate rigidity and tremor) impulses are rivals for the use of the pyramidal tracts and that the preoccupation of the pyramidal tract by the "pathological" impulses detracts from its ability to convey the few, and exquisitely timed, impulses whose arrival at the periphery results in the smooth execution of the tiniest dictates of the will. It is only when a great surge of impulses is initiated that the pathological impulses are swamped or blocked, and the arrival of such an avalanche of impulses at the final common path can result only in a larger or coarser movement. Hence it is that ability to perform delicate and fine movements is lost, and the face becomes a mask. All movements are difficult, as now a correspondingly large effort of will is needed to clear the pyramidal tract before any motor act is possible.

The cerebral cortex is believed by Fulton [14] to be a "common focus of integrations of the extrapyramidal systems both of the striatum and of the cerebellum and through thus co-ordinating the postural with the phasic mechanism absolute smoothness and precision of actions are made possible."

PHARMACOLOGY OF AMYL NITRITE

Leech [15] (1893), in his Croonian lectures for 1893, described how solutions of the inorganic nitrites of 1 : 1,000 dilution caused the contractions of the isolated frog gastrocnemius muscle to become progressively weaker, so that the muscle failed to respond to stimulation by an electric current after 30 to 40 minutes, whereas the control muscle in isotonic sodium chloride solution was still capable of responding to stimuli by contraction after 24 hours. He also found that the O-N-O radical decreased the contractile power of muscular tissue and the duration of its viability. In further experiments, he found that the functions of the spinal cord were also depressed by the nitrite radical. The diminution of reflex activity caused by amyl nitrite was never preceded by functional excitement.

Cash and Dunstan [16] (1893) investigated the physiological actions of the organic nitrites and also concluded that the characteristic effects were due to the nitroxyl group. They also drew attention to the fact that the material used in medicine under the name of amyl nitrite is highly impure in that it contains a high proportion of other alkyl nitrites, notably ethyl, propyl and butyl nitrites, as well as their oxidation products. Though this observation was made in 1893, it remains substantially true today. These investigators also found that very small doses of amyl nitrite, such as 0.01 cc., tended to weaken and ultimately to abolish the active contraction of a standard nerve-muscle preparation in response to stimulation. Large doses, however, produced rigor in the preparation. The authors established, however, that minute doses of the nitrite, insufficient to cause decided shortening, interfered with active contraction and caused the muscle to fail to respond to stimulation, whereas a conrol preparation under identical conditions except that isotonic sodium chloride solution replaced the amyl nitrites continued to respond to stimulation.

14. Fulton, J. F.: Physiology of Nervous System, ed. 2, Oxford University Press, New York, 1943.

15. Leech, D. J.: Lancet **1**:1499; **2**:3, 76, 123 and 177, 1893.

16. Cash, J. T., and Dunstan, W. R.: Phil. Tr. (1893) **184B**:505, 1894.

The ability of the nitrites to increase the pulse rate increases with the molecular weight and from primary to tertiary compounds. Therefore, as far as the vasodilating action, and hence the lowering of the blood pressure, is concerned, it would appear that it is the number of the alkyl groups that is of importance, since the percentage of the O-N-O radical decreases as the series is ascended. Atkinson [17] found the reflex activity of the spinal cord to be lowered by sodium nitrite and by amyl nitrite. It has been shown, however, that the tremor-inhibiting action is not related to the degree of lowering of the blood pressure.

Experiments were conducted on Miss S. in an attempt to ascertain whether the action of the amyl nitrite was partly peripheral; but as these studies were inconclusive, they have not been reported in detail. It must be noted that, although there may be general vasodilatation and a fall in blood pressure, the cerebral blood flow may in fact increase, as was shown to occur in six of eight human subjects after the administration of various vasodilating drugs, including amyl nitrite, by Gibbs, Gibbs and Lennox.[18] In view of this observation, it might well be that an increased cerebral blood flow may account for some degree of functional recovery of the damaged parts or of improved efficiency of undamaged parts and so allow of a return to normality and the disappearance of the tremor.

Gardner and Williams [19] (1949) treated a series of patients with Parkinson's disease of all types by means of bilateral stellate ganglionectomy, which they regarded as producing cerebral vasodilatation. However, they found no significant change in the tremor or rigidity in any of their 34 cases.

Further support for the central effects comes from Schüller [20] (1874), who observed the dilatation of the cortical vessels in rabbits directly. Wolff [21] (1929) found that dilatation of the pial vessels (both arteries and veins) occurred with a rise in cerebrospinal fluid pressure and a fall in the blood pressure. He also noticed that the blood was chocolate colored, presumably owing to the production of methemoglobin, which substance Cushny [22] suggested may be partly responsible for for the convulsions sometimes seen in animals after large doses under experimental conditions.

From the foregoing discussion, it would appear that amyl nitrite is capable of temporarily inhibiting the tremor of parkinsonism in certain cases. There are grounds for considering that, though an increase in total cerebral flow is the most probable explanation, a peripheral mechanism cannot be entirely discounted. In view of the chemical impurity of the pharmaceutical amyl nitrite, further investigation using pure preparations of other members of the alkyl nitrite series may profitably be undertaken.

Dr. Denis Hill cooperated in the early stages of the study; Dr. MacDonald Critchley gave helpful criticism, and Dr. Clifford Hoyle helped in the preparation of the paper.

17. Atkinson, G. A.: Abstract, J. Anat. & Physiol. **22**:225, 1887.

18. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Am. Heart J. **10**:916, 1935.

19. Gardner, W. J., and Williams, G. H., Jr.: Interruption of the Sympathetic Nerve Supply to the Brain—Effect on Parkinson's Syndrome, Arch. Neurol. & Psychiat. **61**:413 (April) 1949.

20. Schüller, M.: Klin. Wchnschr. **2**:294, 1874.

21. Wolff, H. G.: Cerebral Circulation: Action of Amyl Nitrite, Arch. Neurol. & Psychiat. **22**:695 (Oct.) 1929.

22. Cushny, A. R.: Pharmacology and Therapeutics, ed. 13, Philadelphia, Lea & Febiger, 1947.

DEATHS RELATED TO PNEUMOENCEPHALOGRAPHY DURING A SIX YEAR PERIOD

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DEATH does not follow pneumoencephalography in normal persons, although air embolism may have been the cause of two deaths reported by King and Otenasek.[1] Deaths are known to occur, however, after pneumoencephalography in persons who are not normal. Davidoff and Dyke [2] reported nine fatalities in their series of 4,000 cases, a mortality of 0.22 per cent. One of their patients, with a normal pneumoencephalogram, died of a coronary occlusion six hours after the procedure. They concluded that "patients who are likely to succumb to the procedure are those harboring intracranial tumors, aneurysms, or are suffering from arteriosclerotic disease of the brain or elsewhere." They advised ventriculography for patients with clinical signs of increased intracranial pressure and pneumoencephalography for all other patients in need of such a test.

The recent occurrence of deaths following pneumoencephalography at the Neurological Institute of New York suggested a review of the circumstances attending such fatalities at this institution, in order that the risk might be better defined. Twenty-four deaths were found in a series of 2,490 pneumoencephalographic studies performed during the six year period from Jan. 1, 1943 to Jan. 1, 1949.[3] Davidoff and Dyke [2] noted that "the exact estimation of the death-rate in the literature is difficult since deaths from ventriculography and encephalography are often not differentiated. Moreover, the criteria by which a death is considered as related or not related to the encephalographic procedure vary from clinic to clinic." Ghersi [4] reported a death one hour before the time scheduled for the performance of the pneumoencephalographic study, from rupture of an aneurysm, and pleaded for consideration of coincidence in mortality statistics.

For the present study, death was considered to have been related when deterioration in the clinical condition began after the procedure and continued uninter-

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1. King, A. B., and Otenasek, F. J.: Air Embolism Occurring During Encephalography: Report of 2 Cases, J. Neurosurg. **5**:577-579, 1948.

2. Davidoff, L. M., and Dyke, C. G.: The Normal Encephalogram, ed. 2, Philadelphia, Lea & Febiger, 1946, p. 46.

3. The number of procedures performed in each year was obtained from records of the roentgenology department of the Institute.

4. Ghersi, J. A.: Lo que pudo ser consignado como un accidente encefalográfico, Prensa méd. argent. **33**:528-529, 1946.

rupted until death, after a short period. Six of the 24 deaths were in this category (table 1). Deaths following the pneumoencephalographic procedure which were considered unrelated (table 1) occurred weeks or months later or followed intercurrent disease.

MATERIAL

Table 2 presents the incidence of deaths related to pneumoencephalography during the period studied. Summaries of the six cases follow.

CASE 1.—*A woman aged 50 with parasagittal meningioma; death 55 hours after pneumoencephalography.*

The patient was admitted July 5, 1944 with a history of occipitofrontal headache, severer on the left side, and unsteadiness of gait for 18 months and of emesis with a period of stupor for two months. Examination revealed unsteadiness of gait; falling to the left in the Romberg posi-

TABLE 1.—*Categories of Cases According to Relation of Pneumoencephalography to Death*

Category	Deaths
Pneumoencephalography unrelated	9
Surgical procedure after uncomplicated pneumoencephalography	4
Combined pneumoencephalography and ventriculography	3
Pneumoencephalography performed as desperate measure	1
Data insufficient	1
Pneumoencephalography related	6
Total	24

TABLE 2.—*Incidence of Deaths in Relation to Pneumoencephalography*

Year	Total No. of Procedures	No. of Related Deaths	Percentage
1943	451	0	0.0
1944	465	2	0.4
1945	428	1	0.2
1946	439	0	0.0
1947	325	1	0.3
1948	382	2	0.5
Totals (6 yr.)	2,490	6	0.24

tion; terminal tremor in the finger to nose test; ataxia on the left in the heel to knee test; slight drift of the left arm; pallhypesthesia in both legs; diminished proprioception in the left leg; hyperreflexia bilaterally; a Babinski sign bilaterally, more pronounced on the left side; a slow pupillary reflex to light, and slight euphoria. There was no papilledema. The blood pressure was 120/70. The working diagnoses were (1) dementia paralytica, perhaps of tabetic form; (2) cerebellar neoplasm, and (3) (before pneumoencephalography) an "expanding intracranial lesion." Lumbar puncture yielded fluid under an initial pressure of 12 cm., with a protein content of 52 mg. per 100 cc., and 2 white blood cells per cubic millimeter.

The electroencephalogram revealed no focal signs and was considered within normal limits. The indication for pneumoencephalography was the evidence of an "expanding lesion." With the technic used 75 cc. of cerebrospinal fluid was replaced with 70 cc. of oxygen by exchange of 10 cc. volumes after the first 15 cc. Scout films taken after exchange of 20 cc. showed no gas in the ventricular system. According to the roentgenologic report, no gas was seen in the ventricles, but there was a small amount of gas in the cisterna pontis and beneath the tentorium. The cisterna chiasmatis and cisterna interpeduncularis were obliterated. The pineal body was displaced downward into the incisura. Localization was not possible.

The blood pressure rose to 180/100 seven hours after the pneumoencephalographic procedure. On the day after the pneumoencephalogram was taken no blood pressure was recorded. Urinary

incontinence appeared during the night. On the second day after the procedure grunting, Cheyne-Stokes respirations and stupor appeared. There were anisocoria, the left pupil being larger than the right, and left hemiplegia. There was no fever. A ventriculogram revealed that cerebrospinal fluid in the left lateral ventricle was under "great pressure." The right lateral ventricle could not be entered. Despite use of the respirator and stimulants, the patient died 20 minutes after her return to the ward after the ventriculographic procedure and 55 hours after the pneumoencephalographic study.

Autopsy revealed a meningioma, 5.5 cm. in diameter, lying parasagitally in the right parietal region, with compression and degeneration of the right postcentral gyrus, superior parietal lobule, paracentral lobule, gyrus cinguli and gyrus precuneus, herniation of the right gyrus cinguli beneath the falx and of the right uncus through the incisura of the tentorium, compression of the hypothalamus and cerebral peduncles and herniation of the cerebellar tonsils through the foramen magnum with compression of the medulla.

CASE 2.—*A man aged 27 with a clinical diagnosis of hemangiomatosis; death 20 hours after pneumoencephalography.*

The patient was admitted Oct. 18, 1944, with a history of left homonymous hemianopsia for 12 months, ptosis of the right eyelid for eight months and weakness of the left side of the face for three months.

Examination revealed a generalized distribution of small nevi; slight hyperreflexia on the left side; weakness of the left side of the face, left homonymous hemianopsia, anisocoria, the pupil of the left eye being larger than that of the right; ptosis of the right eyelid, scleritis and vascularization of the conjunctiva bilaterally. Vessels of the right fundus were engorged, lengthened and tortuous. The blindspot on the left appeared enlarged as plotted on the tangent screen. The blood pressure was 110/70. The working diagnoses were hemangiomatosis, angiomatosis retinal (von Hippel's disease)? and cutaneous nevi.

Initial roentgenograms showed that the right optic foramen was enlarged, indicating involvement of the optic nerve by a mass, probably a tumor. Lumbar puncture was not performed. The electroencephalogram showed an essentially normal record, without focal signs. A pneumoencephalogram was thought to be indicated because of the focal signs on the left side. According to the exchange technic, cerebrospinal fluid was replaced by oxygen in 5 cc. volumes until 35 cc. of the cerebrospinal fluid had been exchanged for 45 cc. of oxygen. Scout films showed good filling. The roentgenologic report stated that there was incomplete filling of the ventricular system, which was definitely displaced to the left of the midline. Filling was insufficient for localization. The impression was that of an expanding intracranial lesion on the right side, probably an extension of the hemangioma from the right orbit.

After 35 cc. of cerebrospinal fluid had been removed by the procedure, there was a tonic convulsive seizure, during which the head turned to the left, the lower extremities were hyperextended and the right elbow was extended, with wrist and fingers flexed; the left upper extremity was in extreme flexion at all joints. The seizure diminished under the administration of amobarbital sodium U. S. P. (0.75 Gm.) intravenously and open drop etherization. The patient remained in a tonic spastic state on return to the ward, with bilateral ankle clonus, fixed pupils, corneal anesthesia, a blood pressure of 150 to 160 systolic and 80 to 90 diastolic and a pulse rate of 90. He was transferred to the surgical room at 4:30 p. m. Trephination was performed in the right occipital area, and contents of a hematoma were obtained, under pressure, from a depth of 6 cm. It was noted that the bone was unusually vascular and that the pial vessels appeared widely dilated. At 7 p. m., despite stimulants, he was unresponsive, and there was extensor rigidity of both lower extremities and of the left upper extremity. By 10:30 p. m., his temperature had risen to 105 F., his pulse rate was 110 and he had been incontinent of urine. He became cyanotic and died at 5:15 a. m., on the morning of the first day after the pneumoencephalographic procedure, 20 hours after its performance. Permission for autopsy was not obtained.

The final diagnosis was generalized cerebral hemangiomatosis on the right side, involving also the right orbit. Surgical procedures were trephination in the right posterior parietal area, with needle drainage of an intracerebral hematoma, and encephalography.

CASE 3.—*A man aged 66 with a parasagittal meningioma; death 52 hours after pneumoencephalography.*

The patient was admitted April 16, 1945 with a history of fatigability and somnolence for five months, frontal headache and "dizzy spells" for four months, weakness of the left arm for three months and of the left leg for two months, memory loss and a defect (homonymous?) in the left visual field. The percussion note was dull over the right side of the cranium; associated movements were diminished in the left arm; the left leg dragged; there were weakness and "clumsiness" of the left arm, falling to the left, hyperreflexia and a Babinski sign in the left leg, absence of abdominal and cremasteric reflexes on the left, questionable diminution in two point discrimination in the left arm, diminished proprioception in the left leg, papilledema (1 to 2 D. in each eye), left homonymous hemianopsia and weakness of the left lateral rectus muscle. The patient was underproductive and depressed. The working diagnosis on his admission was an expanding intracranial lesion, probably a neoplasm in the right parietotemporal region, and on his transfer to the operating room it was changed to meningioma in the right parietal area.

Initial roentgenograms showed an increase in vascularity and hyperostosis high in the right parietal bone, indicating a meningioma located in the region. Lumbar puncture yielded fluid under an initial pressure of 21 cm., with a protein content of 70 mg. per 100 cc., and 1 white cell per cubic millimeter. The electroencephalogram showed focal signs on the right, being clearest over the postcentral area. Pneumoencephalography was considered indicated "to prove the size of the lesion." The exchange technic proceeded "in a fractional manner" until 25 cc. of cerebrospinal fluid was removed and 20 cc. oxygen was injected. A scout film showed no air in the ventricles, and the procedure was discontinued. The roentgenologic report stated that the attempt to obtain an encephalogram was unsuccessful.

The patient was returned to the ward at 10:40 a. m. At 8 p. m. his reactions were noted to be sluggish. By 11 p. m. he was semicomatose. The blood pressure was 135/95, and the pulse rate was 68 per minute. By midnight he was unconscious and did not respond to supraorbital pressure. At 9:30 a. m. of the first day after the procedure, the blood pressure was 148/72, the pulse rate was 88, the respiration rate was 30 per minute and the temperature was 100.4 F. At 10:15 a. m., because of apnea and cyanosis, he was placed in a respirator, and 15 minutes later a craniotomy was performed in the right occipital area. A large tumor was almost completely removed. The patient remained apneic and comatose, with a pulse rate of 80 and fixed pupils; despite use of stimulants and intravenous administration of plasma, he died the following day, 24 hours after craniotomy and 52 hours after the pneumoencephalographic procedure. Autopsy revealed a meningioma, 5.5 cm. in diameter, located parasagittally in the right parietal region, with invasion of the leptomeninges and cortex. There were compression of the right parietal lobule, herniation of the right uncus and hippocampal gyrus into the incisura of the tentorium, compression of the hypothalamus and midbrain, hemorrhage into the midbrain and pons, acute necrosis of the anterior lobe of the pituitary and a choristoma of the posterior lobe of the gland.

CASE 4.—*A woman aged 46 with a clinical diagnosis of tumor of the brain stem; death 4½ hours after pneumoencephalography.*

The patient was admitted Feb. 25, 1947 with a history of frequency and urgency of micturition and nocturia of 12 months' duration; loss of ambition and energy, with depression and forgetfulness, of 6 months' duration, and numbness of the toes on the right, followed by numbness of the foot, leg and hand, of 2 months' duration. Examination revealed paresis and dragging of the right leg, diminished associated movements of both arms, downward and outward drift of the right arm and terminal tremor in the right arm in the finger to nose test. Succession movements could not be performed with the right leg, and were poorly done with the arms, especially on the right. There was hyperreflexia with ankle clonus on the right. Proprioception was diminished in the right arm and leg, especially in the right foot. There were loss of memory and acalculia. The blood pressure was 165/100. Vision was 20/15 in each eye. The visual fields and optic disks were later reported to be normal. The working diagnoses were (1) glioma of the left frontoparietal region with involvement of the corpus callosum; (2) suspected parasagittal tumor of the premotor area or the upper part of the brain stem, and (3) degenerative disease.

Initial roentgenograms showed hyperostosis frontalis interna of moderate degree. Lumbar puncture was not performed. An electroencephalogram showed transient slowing in the midline parietal area, of doubtful significance. One observer stated: "There is an almost conclusive picture of neoplasm, probably astrocytoma. . . . Air studies are indicated, but the picture is so clear that even if they were noncontributory exploration would be advisable." Since the history and the optic disks did not suggest "an effectual increase in general intracranial pressure," encephalography was recommended by another observer. Sixty cubic centimeters of cerebrospinal fluid was replaced by 60 cc. oxygen. The roentgenologic report stated that only a small amount of the gas entered the right lateral ventricle and that a fairly large amount of gas was collected in the subtentorial region. On the scout films the fourth ventricle could be seen to contain gas and to be in a midline position. Filling of the ventricles above this level was not sufficient to demonstrate the presence or absence of a shift of the ventricles. The basal cisterns showed no abnormalities. The pneumoencephalogram was considered unsatisfactory.

At 1:10 p. m. on the day of the procedure the blood pressure was noted to be 206/110, the pulse rate 96, the temperature 99 F., and the respiration rate 22. During the course of 10 minutes the patient passed from a state of restlessness and incoherence to one of coma; the left eye deviated laterally and became dilated. Five minutes later the right eye became dilated. The neurosurgical consultant thought the diagnosis was that of a "tumor of the brain stem, probably in the thalamus." By 2:15 p. m. there was cyanosis, and on the patient's arrival in the operating room, at 2:20 p. m., she was apneic. A trephination was performed in the right occipitoparietal area, without sterile precautions because of the emergency, and clear, colorless fluid mixed with some gas was obtained from the right lateral ventricle, under "great pressure." From 10 to 15 cc. of fluid was removed slowly. Despite the use of artificial respiration and stimulants, including intracardiac administration of epinephrine, the patient was pronounced dead at 2:45 p. m., four hours and 30 minutes after the procedure. Permission for autopsy was not obtained.

The final diagnoses were tumor of the brain stem and herniation of the cerebellar tonsils.

CASE 5.—*A man aged 51 with a meningioma of the sphenoidal ridge; death 57 hours after pneumoencephalography.*

The patient was admitted May 25, 1948, with a history of recurring episodes of weakness, accompanied with sensations of impending disaster and disorientation and ushered in by gustatory hallucinations, for 2½ years. Syncope occurred three months before his admission, with postictal disorientation and headache. Depression, sluggishness and loss of memory had been present for one year. There was slight hyperreflexia in the left leg; the abdominal reflex was slightly more active on the right than on the left, and an equivocal Babinski reflex was present on the left, elicited by reenforcement with the Oppenheim maneuver. The optic disks and visual fields were normal. The blood pressure was 130/80. The working diagnoses were (1) cerebral arteriosclerosis, a lesion in the subfrontal or the temporal lobe to be ruled out; (2) infiltrating cerebral lesion on the right, and (3) intraventricular meningioma, right temporal horn. The initial roentgenogram stated that vascular channels along the left coronal suture were prominent. Minimal demineralization of the posterior clinoid processes was present. Lumbar puncture showed an initial pressure of 16 cm., with a protein content of 420 mg. per 100 cc. and a white cell count of 2 per cubic millimeter. An electroencephalogram showed a clearcut focus in the right temporal area.

One observer stated: "In view of an absence of increased intracranial pressure, I feel that a pneumoencephalogram may safely be done, and I recommend it as the most satisfactory diagnostic measure now." Another stated: "Despite the absence of papilledema, with a spinal fluid protein of 420 mg. I feel that an arteriogram or a ventriculogram, rather than a pneumoencephalogram, should be obtained." The exchange technic was not noted; 85 cc. of cerebrospinal fluid was exchanged for 80 cc. of oxygen. Scout films showed a shift of the lateral ventricle. The roentgenologic report stated that both lateral ventricles and the third ventricle were displaced to the left, the right frontal horn and body herniating under the falx. The left lateral ventricle was somewhat enlarged. The temporal horn on the right was never filled with air beyond its most proximal stump. The latter appeared to be slightly elevated and participated in the shift of the ventricular system to the left side. The aqueduct and the fourth ventricle

were poorly outlined but showed no gross abnormalities in position. The impression was that of a large space-occupying lesion in the right temporal lobe.

By 1 p. m. on the day of the procedure the patient was drowsy and confused, and exhibited cyanosis and diaphoresis. The blood pressure was 130/80 and the pulse rate 76. By 2 p. m. he was in a state of moderate shock, with a blood pressure of 112/78. He was given oxygen by nasal catheter (3:30 p. m.) and caffeine and sodium benzoate intramuscularly. His temperature rose to 103 F. (6 p. m.), and his blood pressure fell to 96/68 (9 p. m.). He improved somewhat during the night but was transferred to the surgical floor at 3 p. m. on the first day after the pneumoencephalographic procedure. Here it was noted that his blood pressure was 130/80; there were moderate left hemiparesis, downward drift of the left arm and diminished succession movements in that extremity. He was drowsy, depressed, underproductive and slow to respond to stimuli. That night he began to hiccup, and this continued until his death, which occurred despite administration of carbon dioxide by mask and rebreathing. His temperature remained elevated (103.6 F.). On the second day after the procedure he was more lethargic, and the hemiparesis had increased in severity and involved the face. His blood pressure was 112/78. With the local use of thiopental anesthesia, exploration of the right frontotemporal region was begun at 3 p. m. Neoplastic tissue was encountered in the temporal lobe, and partial temporal lobectomy was necessary to enucleate the tumor. Oozing and hemorrhage were profuse during the procedure. The axillary temperature rose to 107; the respirations became gasping; the pulse rate rose to 160 per minute; the blood pressure became unobtainable, and despite administration of plasma and gelatin intravenously, the patient died at 8:30 p. m., a few minutes after being placed in an artificial respirator and 57 hours after the pneumoencephalographic procedure. Permission for autopsy was not obtained.

The final diagnosis was deep meningioma of the right sphenoid ridge. Operations included exploration of the right frontotemporal area, partial temporal lobectomy, and enucleation of a meningioma. The pathological report stated that the specimen was identified as a meningioma, measuring 5 by 5 by 2.5 cm.

CASE 6.—*A man aged 55 with a glioblastoma on the left side; death 97 hours after pneumoencephalography.*

The patient was admitted July 23, 1948, with a history of episodes of transient weakness, accompanied with feelings of unreality, of seven months' duration; transient numbness of the right arm for seven months; weakness of the right leg for seven months; weakness and clumsiness of the right arm and leg for three weeks, and bifrontal headache for one day. Examination revealed right hemiparesis, strong downward drift of the right arm, slight terminal ataxia in that member, hyperreflexia on the right side, a 1 + Babinski sign on the left and slight flattening of the nasolabial fold with weakness of the platysma on the left. The patient was depressed and underproductive. There were questionable blurring of the optic disk and venous engorgement on the right. The working diagnosis was that of an expanding infiltrating subcortical or parasagittal lesion. Initial roentgenograms showed no abnormalities. Lumbar puncture yielded fluid under an initial pressure of 12 cm. with a protein content of 70 mg. per 100 cc., a white cell count of 1 and a red cell count of 5 per cubic millimeter. Electroencephalography was not carried out. Indications for pneumoencephalography were not stated. The exchange technic was not noted, but 60 cc. of cerebrospinal fluid was exchanged for 55 cc. of oxygen. The roentgenologic report stated that deformity of the lateral ventricles was pronounced. A large filling defect extended from the anterior horn to the posterior third of the body of the lateral ventricle bilaterally. The deformity was produced from the superior side, with pronounced depression of the ventricular roof of these areas, but the ventricular lumen was not occluded completely. The third ventricle was poorly outlined. The aqueduct and the fourth ventricle were normal. The impression was that of a large bilateral mass superior to the ventricles, extending from the level of the anterior horn to the posterior part of the body in the frontoparietal area.

The blood pressure, pulse rate, respiration rate and temperature were unchanged, but by 7:30 p. m. on the day of the procedure the patient was stuporous. Physical signs included complete spastic hemiplegia of the right side, involving the face, with strong hyperreflexia. There was weakness of the left side, with Hoffmann and Babinski signs. Trephination was performed in the left frontotemporal area at 10 p. m., and biopsy showed glioblastoma multiforme. On the

first day after pneumoencephalogram and trephination the patient was semicomatose and incontinent of urine. On the second day his temperature had risen to 102 F. and he became incontinent of feces. On the third day his temperature was 105 F. and his pulse rate 144. He died at 1:10 p. m., 97 hours after pneumoencephalography. Autopsy revealed glioblastoma multiforme involving the left frontal and parietal lobes, the corpus callosum and the right caudate nucleus (5 by 6 cm.), with herniation of the left cingulate gyrus beneath the falx, and of the unci and hippocampal gyri through the incisura tentorii, this change being more conspicuous on the left. There were also compression of the hypothalamus and midbrain, herniation of the cerebellar tonsils through the foramen magnum and recent hemorrhages into the neoplasm and left lateral ventricle.

ANALYSIS OF CASE MATERIAL

The pertinent facts obtained from the analysis of the six cases in which death was considered to be related to the procedure are enumerated as follows:

1. The mortality rate (six cases in 2,490 procedures) of 0.24 per cent corresponds closely to that of 0.22 per cent reported by Davidoff and Dyke.[2]

TABLE 3.—*Principal Diagnosis in Cases in Which Pneumoencephalography Was Related to Death*

Case	Age	Year	Diagnosis	Pathological Data
1	50	1944	Parasagittal meningioma	Autopsy
2	27	1944	Cerebral hemangiomatosis	.....
3	66	1945	Parasagittal meningioma	Autopsy
4	46	1947	"Brain stem tumor"	.....
5	51	1948	Sphenoid ridge meningioma	Operation
6	55	1948	Glioblastoma of frontal and parietal regions	Autopsy

TABLE 4.—*Time Elapsing Between Pneumoencephalography and Death*

Case no.....	6	5	1	3	2	4
Time elapsing, hr.....	97	57	55	52	20	4½

2. Large space-occupying lesions were present in all the six cases in which death was related to the pneumoencephalographic procedure. Five were cellular neoplasms and one was a vascular lesion, presumably a neoplasm. Five of the six lesions [5] were supracallosal, and one was located in the temporal lobe. The absence of deaths associated with subtentorial tumors in this series is probably related to the observance of a policy contraindicating pneumoencephalography when such lesions are suspected.

3. The period between performance of the test and death varied from 4½ to 97 hours. There was a remarkable similarity in the time elapsing between pneumoencephalography and death in the three cases with large meningiomas (cases 1, 3 and 5, table 4).

4. In four of the six cases there was evidence of increased intracranial pressure (table 5). In two cases there was a mild degree of papilledema, and in three there were changes in the roentgenograms indicating the possibility of an expanding intracranial lesion.

5. Diagnosis was established by autopsy in three cases, by operation in one case and by clinical data in one case.

5. Except in case 2, no symptoms occurred during the actual pneumoencephalographic procedure to distinguish the six fatal cases from those in which there were no complications. In case 2 (presumably one of a vascular neoplasm) a seizure occurred with the needle in place.

6. A rise in the blood pressure following pneumoencephalography is an ominous sign. It occurred in three of the six cases, and its significance was unheeded in case 1.

7. In two of the four cases in which lumbar puncture was done before the pneumoencephalographic study the intracranial pressure was below 15 cm. In the other two cases (cases 3 and 5) the readings were 21 and 16 cm., respectively.

8. In only one of four cases in which lumbar puncture was done was there an increase in the spinal fluid protein content, although all were cases of neoplasm and in 3 the presence of meningioma was proved. In case 5, that of meningioma of the sphenoid ridge, the protein content was 420 mg. per 100 cc.

TABLE 5.—*Signs of Increased Intracranial Pressure Before Pneumoencephalography Which Was Related to Death and Additional Signs After Procedure*

Case	Signs Present Before Procedure	Additional Signs After Procedure
1	Headache; pineal displacement	Hypertension; stupor; Cheyne-Stokes respiration; incontinence; increased ventricular fluid pressure
6	Headache; papilledema	Stupor; incontinence
5	Prominent vascular channels; demineralization of posterior clinoid processes	Confusion; cyanosis; singultus (hiccup); lethargy
3	Headache; papilledema; roentgenologic changes suggesting meningioma; cerebrospinal fluid hypertension (21 cm. of fluid)	Coma; apnea; fixed pupils
2	None	Coma; hypertension; incontinence; cyanosis; blood in ventricle, under pressure
4	None	Coma; hypertension; apnea; greatly increased ventricular fluid pressure

COMMENT

This study confirms the danger attending pneumoencephalography in patients with intracranial tumors, but indicates that absence of signs of intracranial hypertension (cases 2 and 4) is not security against complications.

The number of patients on whom the pneumoencephalographic procedures were performed who actually harbored neoplasms is not known and could be obtained only with much difficulty. The incidence of deaths from the procedure in patients having neoplasms is not as significant as the circumstances of the individual death. In at least two of the six cases the lesions were operable, and there was a fairly good postoperative prognosis. Surgical treatment under emergency circumstances is always to be avoided, and careful evaluation of symptoms and signs before pneumoencephalography is elected may prevent such a necessity. No attempt was made in this study to collect cases in which rapid worsening in the clinical condition followed pneumoencephalography but surgical intervention was successful and death did not ensue. The incidence of such cases may not be negligible.

The information in table 6 suggests that the physiological consequence of a pneumoencephalographic study which may produce death is a change in anatomic

relations of intracranial structures such that function of vital nuclei or tracts is no longer possible. Ischemia may follow vascular distortion and compression. The change in anatomic relations cannot be solely the result of substituting gas for ventricular fluid, for in case 3 only 20 cc. of gas replaced 25 cc. of fluid, and none of the gas entered the ventricular system.

TABLE 6.—*Pathological Indications of Disturbed Intracranial Pressure Relations in Three Cases of Death After Pneumoencephalography for Which Autopsy Reports Are Available*

	Number of Cases
Compression	
Of tissue adjacent to tumor	2
Of hypothalamus	2
Of midbrain	2
Of cerebral peduncles	1
Of medulla	1
Herniation	
Of uncus through incisura of tentorium	3
Of cingulate gyrus beneath the falx	2
Of hippocampal gyrus through incisura	2
Of cerebellar tonsils through foramen magnum	2

SUMMARY AND CONCLUSIONS

Six cases of death related to pneumoencephalography in a series of 2,490 procedures during a six year period (mortality 0.24 per cent) are evaluated with regard to clinical and pathological circumstances. It is recognized that the condition of patients with tumors of the brain may suddenly become grave for no apparent reason, and that similar deterioration, or death, may follow ventriculography or arteriography. It is concluded, however, that one of these procedures should be elected for patients in whom the clinical evidence supports a diagnosis of space-occupying intracranial lesion, probably large, and supracallosal or temporal in location. For such patients pneumoencephalography should not be elected unless the patient has been prepared for such immediate surgical treatment as may be indicated by the results of the study.

Dr. E. H. Wood Jr., assistant professor of radiology, Columbia University College of Physicians and Surgeons, and Mrs. M. C. O'Neil, chief x-ray technician, Neurological Institute, gave assistance in this study.

INTERACTION IN BILATERALLY SIMULTANEOUS VOLUNTARY MOTOR FUNCTION

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IT IS NOW well recognized in the sphere of sensory perception that percepts as determined by a single stimulus may be altered, or even obliterated, when disparate multiple stimuli are simultaneously applied to various regions of the soma.[1] This phenomenon has been demonstrated most clearly in the modalities of vision, audition and general cutaneous sensory function.

It has also been observed that under certain conditions a unilateral Babinski sign can be obliterated with bilateral simultaneous plantar stimulation [2]; occasionally bilateral simultaneous plantar stimulation is also seen to enhance a weak or equivocal unilateral Babinski sign.

In the sphere of voluntary executive function interaction influences have not yet been specifically demonstrated. The purpose of this presentation is to show that interaction in the motor sphere does occur and can be demonstrated by suitable means.

Succession movements, or the diadokokinetic action of Babinski,[3] lend themselves admirably to the study of motor interaction. It was clinically observed that certain patients with hemiparesis who had diminished supination-pronation ability on the involved side often showed impaired supination-pronation movements of the intact side when these actions were executed simultaneously on the two sides. This effect was particularly well brought out when the patient was exhorted to operate at maximum speed of alternation and when the patient had a desire to excel! The primary major effect of bilateral simultaneous supination-pronation action was to decrease the ability of the intact side to perform with the facility that was evident when the intact side alone was set into operation.

PRESENT INVESTIGATION

In order to make relatively precise observations of this phenomenon, two methods of study were employed. One was by means of motion picture photography; the other, by means of a photocell transducer system operating into an ink-writing oscillograph. The latter system was eminently practical because of the simplicity and the definition of its output. A schematic diagram of the photocell system is shown in figure 1.

From the United States Naval Hospital, Bethesda, Md.

1. Bender, M. B.: Extinction and Precipitation of Cutaneous Sensations, Arch. Neurol. & Psychiat. **54**:1 (July) 1945. Bender M. B., and Teuber, H. L.: Phenomena of Fluctuation, Extinction and Completion in Visual Perception, ibid. **55**:627 (June) 1946.

2. Cohn, R.: The Babinski Sign: Extinction During Bilateral Simultaneous Cutaneous Stimulation, J. Neurophysiol. **11**:193, 1948.

3. Babinski, J.: Sur le rôle du cervelet dans les actes volitionnels nécessitant une succession rapide de mouvements (diadococinésie), Rev. neurol. **10**:1013, 1902.

As noted in the figure, a central lamp was employed as a source of light to activate the laterally placed photocells. The light source was modulated by the rotation of the distal portions of the forearms. In the right-handed normal controls it was observed that the majority of subjects were capable of a supination-pronation action with a rate ranging from 2 to 3 times per second on the right side; similar movements of the left upper limb were slightly, but definitely, lower in frequency, at about 2 movements per second in this series. When the two limbs were set into simultaneous operation, the right ordinarily assumed the rate of action of the slower-moving part. This phenomenon is demonstrated in figure 2.

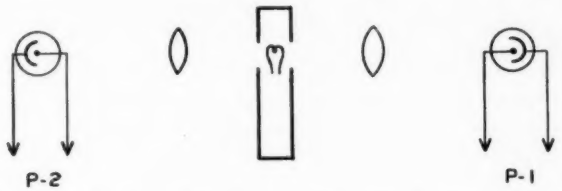

Fig. 1.—Diagram of the photocell and light system for recording supination-pronation movements.

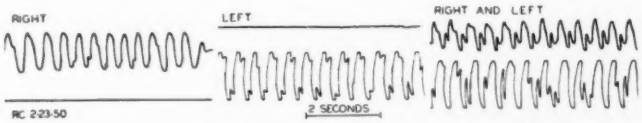

Fig. 2.—Normal control. The right and then the left upper limb are independently activated; finally, the two limbs are set into motion simultaneously. The right limb is more rapid in action than the left. It should be noted that the synchronization in bilateral simultaneous movement is at the frequency of the slower-acting part.

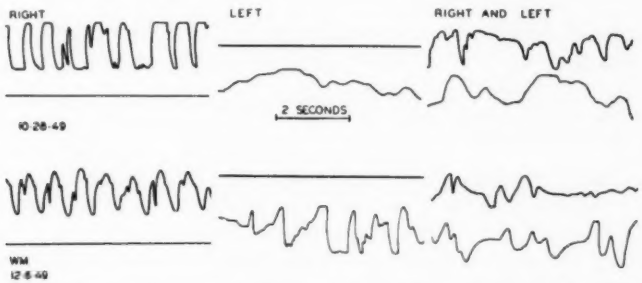

Fig. 3.—Hemiparesis (left). The upper set of tracings was recorded five days after the onset of a vascular accident. The involved side greatly decreases the facility of movement of the intact side when the limbs are activated simultaneously.

In the lower set of lines, despite the clinical return of function in the left upper extremity, a deleterious interaction is exhibited in simultaneous action.

Patients with hemiparesis of either upper limb presented a most remarkable, intense interaction phenomenon. The upper line of the samples of record which comprise figure 3 were obtained from a patient 45 years of age who had suffered from a cerebral vascular accident five days prior to the recording. In the right, or relatively intact, upper limb, supination-pronation action was not rhythmical; it ranged around 1.5 times per second in frequency. The action of the involved (left)

limb was tremendously reduced in amplitude and frequency. When the two limbs were set into simultaneous motion, the action of the right limb was greatly reduced in speed and amplitude of motion as compared with its independent operation. The activity of the involved (left) limb was not appreciably altered, although there was some apparent increase in frequency of movement.

Five weeks later this patient showed relatively good restitution of motor function of the left upper limb. However, it was again recognized that there was a strong tendency for the involved (left) arm almost completely to obliterate the normal function of the intact (right) limb in supination-pronation movement (lower lines of figure 3).

Figure 4 shows the record of a patient who had a lesion of the brain primarily involving the left internal capsule. Here, again, definite interaction was observed when the upper limbs were moved simultaneously in supination-pronation action. The reduction in frequency of movement in the intact (left) limb was only about

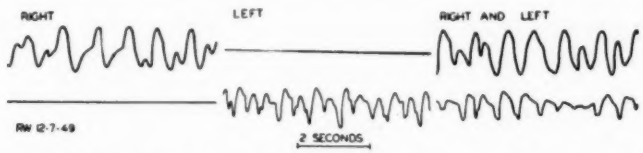

Fig. 4.—Moderate hemiparesis (right). In simultaneous action there is a minimal, but definite, decrease in frequency of movement of the uninvolved part. Amplitude of motion is decreased on the intact side during simultaneous action.

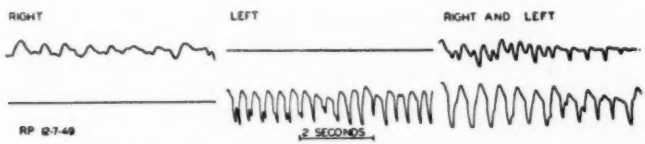

Fig. 5.—Paresis of right upper limb (poliomyelitis). The frequency of movement of the intact limb is decreased, but the action of the involved side is somewhat increased in frequency during simultaneous operation.

½ per second in this instance. It was interesting to note, however, that in the attempt to maintain good action on the involved (right) side the amplitude of the motion on the intact (left) side was greatly reduced.

Paresis of one upper extremity as a result of acute anterior poliomyelitis was also seen to affect the bilateral simultaneous supination-pronation action. Figure 5 shows samples of record from a patient with involvement of the right upper limb. In this instance the frequency of movement of the intact (left) side was reduced by about 1 per second when the extremities were set into simultaneous action. The action of the right limb (involved side), however, was observed to increase both in rhythmicity and in frequency of movement during the simultaneous operation.

In a classic clinical case of occlusion of the posterior inferior cerebellar artery, a strongly deleterious interaction repeatedly resulted when the dystaxic limb was voluntarily set into supination-pronation motion.

It is of major importance to note that if the involved side was so compromised in its action that no motion was possible, even if the paralyzed arm was passively

extended and maintained in proper position for alternating movements, there was absolutely no influence of one on the other; that is, despite attempts to have the patient "feel" that his involved limb was excuting alternating movements, there was no observable effect on the performance of the healthy limb.

In the motion picture recordings of the phenomenon of motor interaction, it was sometimes noted that when the involved side was activated alone there was a strong synkinetic fixation of the relatively intact limb. Occasionally (also demonstrated best in motion pictures) when the patient was strongly urged to increase the rate of movement of the intact limb, the limb of the involved side tended very slowly and very incompletely to operate in a type of mirror synkinesia.

COMMENT

In Babinski's original discussion of diadokokinesia he was primarily concerned with the phenomenon as exhibited with cerebellar lesions. He noted, however, that with simultaneous action of the upper limbs the disturbance of supination-pronation motion became more evident on the involved side. He stated that in hemiparetic extremities "true" adiadokokinesia was not present because the patients had an elementary disability for the performance of succession movements.

In my observations, synchronization, or at least a strong attempt at synchronization, resulted whenever the upper extremities were set into simultaneous motion. In such instances the normal subjects exerted great effort, and experienced much difficulty, in maintaining asynchronous alternating movements. As observed in the sample control recording, synchronization was accomplished by the assumption of the movement of the slower-acting part. In the patients with lesions of the central nervous system that compromised the action of one extremity, it appeared that the attempt to synchronize the motion of the limbs basically produced the disastrous interaction. However, it was also evident, as shown in the figures, that at times this synchronization mechanism functioned to enhance the frequency and amplitude of the supination-pronation action of the involved limb during simultaneous movement. but in these recorded instances it was further observed that the frequency of rotation of the intact side during simultaneous action was reduced from ½ to 1 movement per second as compared with its solo action.

The rate of simultaneous volitional alternating movements appeared to be directly related to the degree of impairment of the involved effector apparatus. In the present series of cases, however, several patients showed mild to even pronounced disturbance in position sense of the fingers of the involved side, but none had difficulty in distinguishing the gross movements involved in supination and pronation. Hence it was impossible to evaluate the precise role of proprioceptive function in the rate and synchronization of simultaneous movements. Nevertheless, it appears that a regulating mechanism operates through the proprioceptive stimuli to the executive apparatus. These effector elements of the network appear, in turn, to be modulated by frontal lobe function in the form of will to initiate and continue the operation of alternating movements.

A precise discussion of the locus of organization for the interaction observed in bilateral supination-pronation movements does not appear possible at present. How-

ever, from the work of Akelaitis,[4] it seems unlikely that the corpus callosum fibers or any other high level interhemispheral connection uniquely subserves the interaction mechanism observed.

The simultaneous movements observed in the study seem to differ markedly from mirror and other complex synergistic actions seen with certain lesions of the central nervous system. The major difference is that the synkinesias are involuntary motions associated with actions of the relatively intact part or are involuntary elementary portions of a total pattern of action.

Deleterious interaction can be strikingly demonstrated in normal subjects when the executive act requires performance on a highly integrated level of function, as in writing simultaneously with the two hands. If the subject is asked to write "cat" with the right hand and "dog" with the left, under ordinary conditions either he is unable to initiate writing, or, once the acts are initiated, he has difficulty in maintaining any semblance of fluidity of movement. Under the latter condition the effective operation primarily consists of the production of successive nonsimultaneous elements of each letter. Often, if great effort is expended, the subject tends to duplicate letters in each word, either in a normal or in a reversed pattern.

If the specific deleterious interaction of bilaterally symmetrical executed movemens of the upper limbs can be generalized, light might be shed on the disturbances in verbalization associated with incomplete destruction of Broca's area in the cortex. It appears reasonable to suppose that the lack of "taking over of the verbalization function" by the subdominant hemisphere in the presence of a crippling lesion of the brain may fundamentally be similar to that demonstrated in the much less complex simultaneous pronation-supination action of the upper extremities.

These data on simultaneous supination-pronation interaction thus bring into sharper focus the idea of Nielsen and Raney,[5] which was attained from purely clinical-pathologic considerations, namely, that the presence of malfunctioning cortex was detrimental to the good function of the remaining, relatively intact cortex. On this basis, they suggested that the ablation of the entire area of the brain subserving the disturbed intercommunication unit might allow unhindered redevelopment of a more effective over-all intercommunication mechanism by the resultant totally uninfluenced cortical functional unit of the intact cerebral hemisphere.

CONCLUSION

It is shown that there is bilateral interaction in the voluntary executive sphere of cerebral function.

4. Akelaitis, A. J.: Studies on the Corpus Callosum: VII. Study of Language Functions (Tactile and Visual Lexia and Graphia) Unilaterally Following Section of the Corpus Callosum, J. Neuropath. & Exper. Neurol. **2**:226, 1943.

5. Nielsen, J. M., and Raney, R. B.: Recovery from Aphasia Studied in Cases of Lobectomy, Arch. Neurol. & Psychiat. **42**:189 (Aug.) 1939.

MIGRAINE AND OTHER HEAD PAIN

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THE SYMPTOM of headache is one of the greatest challenges presented to the practitioner in every field of medicine.[1] Until the past decade the physician was firmly convinced that the average headache was secondary to a specific disease in the body. With this in mind, extensive investigation of the patient was made to rule out any possible sign of organic disease. Once an abnormality of an organ was determined, a vigorous attempt was made to correct this surgically or medically, with the hope that the headache would disappear as a result of these efforts. The actual symptom of headache was minimized by the patient and the physician, and thus the rounds were made to each specialist for investigation in his sphere of activity. Fortunately for these headache sufferers, a considerable amount of physiologic and clinical data has been accumulated in the attempt to determine the mechanism of production of head pain in various disease conditions.[2] Several excellent and comprehensive papers on the general subject of headache have appeared, and these will enable the interested physician to understand the general subject thoroughly.[3] We are now able to present the pathophysiology involved in the mechanism of the majority of headaches dealt with clinically. This, in turn, is used as the basis for a simple, workable classification of headache.

As is true in any other medical condition, the proper diagnosis and treatment in each case of headache must be preceded by a thorough and adequate history, physical and neurologic examinations and appropriate laboratory studies. The

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1. (*a*) Blumenthal, L. S.: Headache: Common Etiologic Types and Methods of Therapy, Am. Pract. **1**:527 (June) 1947. (*b*) Chodoff, P., and Blumenthal, L. S.: Headache—Mechanisms, Differential Diagnosis and Treatment, M. Ann. District of Columbia **16**:295 (June); 372 (July) 1947. (*c*) Woltman, H. W.: The Symptoms of Headache and Some Conditions Suggested by It, Minnesota Med. **23**:19 (Jan.) 1940.

2. Wolff, H. G.: Headache and Other Head Pain, London, Oxford University Press, 1948.

3. (*a*) Horton, B. T., and Macy, D., Jr.: Treatment of Headache, M. Clin. North America **30**:811 (July) 1946. (*b*) Horton, B. T.: Headache: Clinical Varieties and Therapeutic Suggestions, ibid. **33**:973 (July) 1949. (*c*) Butler, S., and Hall, F. R.: The Diagnosis and Treatment of Headache, ibid. **33**:1439 (Sept.) 1949. (*d*) von Storch, T. J. C.: Migraine, 1947: A Review, Am. Pract. **1**:631 (Aug.) 1947.

most important part of this medical investigation is a painstaking and detailed history, which in most circumstances is best taken at several interviews. Although statistics are in general agreement that approximately 50 per cent of all ambulatory patients will present headache as a primary or secondary symptom, the diagnosis made in these cases will vary considerably, depending on whether one studies a group of private patients or a group of clinic patients. At present we are engaged in the evaluation of the cases of headache seen by us during the past year in our private offices and in the headache clinic at the university. The most striking fact so far discovered in this study is the rarity of the true migraine headache in the clinic patient, whereas this type constitutes the large majority of the headache problems which we encountered in our offices.

One of the most important points in the study of a headache problem is the evaluation of the degree of nervous tension present in each case. Mounting nervous tension not only may actually produce headache in many cases but may also aggravate and prolong a headache caused by other factors. The nervous tension is often due to the general life situation of the patient; however, many of these patients are truly concerned as to the nature of their headaches, and this fact tends to make more pronounced the nervous tension present in such cases. We have found that after a complete evaluation of a particular case, and a satisfactory explanation of our findings to the patient, he will be definitely improved as a result of a proper understanding of his case, and the resultant decrease in worry, anxiety and tension that accompany the actual attack of headache, or the anticipation that he might get a headache. In the taking of the clinical history, the patient will often volunteer many facts that will be of aid to the physician in the later handling of the case. One should never belittle the patient's request for a roentgenographic examination of the head or other studies that he may think important in his case, as these requests are often clues to deep-seated fears of brain tumor or other organic lesion.

PATHOPHYSIOLOGY OF HEADACHE

The extensive investigations of pain mechanisms in relation to the structures of the head, in particular the extensive studies of Wolff, as summed up in his recent book on headache,[2] have resulted in our understanding that head pain may originate in one of the following structures: (1) the tissues covering the cranium, (2) the cranial periosteum and endosteum and (3) certain intracranial structures. These pain-sensitive structures in the head are tabulated as follows (after Wolff):

1. Tissues covering the cranium, especially arteries
2. Intracranial structures
   (*a*) Parts of dura mater
   (*b*) Dural arteries
   (*c*) Venous sinuses
   (*d*) Cerebral arteries at base
3. Fifth, ninth and tenth cranial nerves
4. First, second and third cervical nerves

Not only may headache originate in certain structures only, but these structures must be stimulated in certain definite ways to produce the pain. The mechanism

of production of headache from intracranial sources is presented in the accompanying table.

Basic Mechanisms by Which Headache May Arise

Intracranial Sources	Extracranial Sources
1. Traction and displacement of the longitudinal sinus and contributing veins	1. Distention of arteries, chiefly branches of the external carotid artery
2. Traction of the middle meningeal arteries	2. Contraction and spasm of muscles of the scalp and neck*
3. Traction of the arteries of the circle of Willis and its branches	
4. Direct pressure on fifth, ninth and tenth cranial nerves and the upper three cervical nerves	
5. Inflammation in or about any of these structures	
6. Distention and dilatation of intracranial arteries	

* This mechanism may be associated with postural strain, reflexes from pain-sensitive nasal, paranasal and ocular structures, and, especially, tension-anxiety states.

CLINICAL CLASSIFICATION OF HEADACHES

In presenting a clinical classification of headache for general medical use, simplicity and brevity are more important than the inclusion of numerous conditions that are only rarely met with in practice. Numerically speaking, headaches due to nervous tension, psychogenic factors or vasomotor instability of the cerebral blood vessels are found to be more important. However, because most patients with headache fear that they may have a serious intracranial lesion, this category of headache is afforded first place in the classification.

1. Headache due to intracranial disease
   (*a*) Meningeal irritation (meningitis, subarachnoid hemorrhage)
   (*b*) Space-taking lesions (brain tumor, abscess, subdural hematoma)
2. Psychogenic headache
   (*a*) Tension-anxiety
   (*b*) Conversion hysteria
3. Post-traumatic cerebral syndrome
4. Vascular headache
   (*a*) Migraine
   (*b*) Hypertension
   (*c*) Histamine headache
   (*d*) Temporal arteritis
5. Neuralgia
   (*a*) Supraorbital
   (*b*) Occipital-cervical
6. Headache associated with diseases of ocular, nasal and paranasal structures
7. Pyrexial and toxic headache

The position of an internist is to make the diagnosis in each case of headache. Headaches found to be due to neurologic abnormalities, disease of the eyes, ears, nasal or paranasal structures or on a psychogenic basis are referred to the appropriate specialist, as the case may be. Our experience in the treatment of headache, therefore, has been most extensive in the tension, vascular and post-traumatic types of headache. The results of these experiences form the basis of this paper.

TENSION HEADACHE

Nervous tension often plays a large part in the production or prolongation of headache. At times the overlying emotional and nervous tension present in the patient reporting for examination serves to cover or mask any underlying headache

syndrome. The average patient is not in need of any prolonged psychiatric interview or treatment, but he is in need of a physician who is willing to spend the time and energy necessary to uncover the patient's entire story. Once the background and present life situation of the patient are understood, it is simple to evaluate the role of nervous tension.

It will be found that most people subject to such headaches are capable of a certain amount of work, both physical and mental, in each day. It will also be seen how much the patient has exceeded his proper amount of work. He must be instructed in the mechanism of action of excess nervous tension. It is simple to point out to the patient that this tension results in actual spasm and contraction of the muscles about the head and neck, and that when he feels a tight, spastic condition in those areas it is but a red light flickering to warn him that he is exceeding his limits and must relax. This can be likened to a man and his bank account, in which he must have ample funds to cover his drafts on the account. He knows only too well that if he overdraws his account he will soon receive reminders from the bank authorities to that effect, and that if he is to keep solvent, he must replenish his account with additional funds. In this manner, he must be instructed that overdrafts on his nervous system must be replenished by periods of rest, relaxation, exercise and appropriate vacations. He will soon realize that his present difficulties are not directly related to his actions during the immediate past but are due to the accumulation of stresses and the build-up of tension over a prolonged period of time, without proper periods of physical and mental relaxation. Once the patient has an adequate insight into these facts, he might then be permitted to use drugs in the proper amounts. However, he must be made to realize that these drugs are only crutches to aid him in his effort to readjust his activities to his own particular limits, and that the drugs alone will not clear up the entire situation for him. At the beginning, small doses of barbiturates taken three or four times a day will prove of benefit. The use of salicylates, caffeine or the newer caffeine-ergotamine combinations will help to alleviate individual attacks of headache due to nervous tension.

In many of these patients actual tenderness and nodularity of the cervical and scalp muscles are found by palpation. The muscle spasm creating this condition results in an abnormal circulation and an accumulation of metabolites in these tissues. This, in turn, results in pain. It has been found[4] that vasodilators, such as histamine given parenterally or nicotinic acid administered orally or parenterally, will clear up many of these headaches.

This type of patient must be seen repeatedly in order to give him a chance to discuss his problems with the physician, because the more doubts, fears and uncertainties he carries with him, the more tension will develop. Frank discussion and mental catharsis of these problems, although it is time consuming, will prove of great value in improving the general mental condition of the patient and will

4. Williams, H. L.: The Syndrome of Physical or Intrinsic Allergy of the Head: Myalgia of the Head (Sinus Headache), Proc. Staff Meet., Mayo Clin. **20**:177 (June 13) 1945.

help to prevent the attacks of headache from developing. The latter facts are just as important in headaches due to actual vascular, endocrine or traumatic conditions and must be borne in mind in the handling of any case of chronic headache.

VASCULAR HEADACHE

Migraine.—Although many of the newer treatments used in the management of chronic headache are applicable to migraine as well, it is still most important to define what we mean by migraine whenever we discuss headache in general. Without an accurate definition it is impossible to evaluate the ever increasing number of reports concerned with the treatment of migraine. The patient with migraine gives a history of periodic unilateral temporal or orbital pain, with a definite hereditary background of headache, epilepsy or allergy. The pain is often preceded by an aura in the form of scotomas, mental dulness or blurred vision and is accompanied with nausea and often emesis. The headaches are at least twice as frequent in women as in men and usually attack the ambitious members of society. They appear under periods of stress or in definite relation to the menstrual period and in many women disappear during pregnancy and at the climacteric. Ninety per cent of the individual attacks are relieved by the injection of 0.5 mg. of ergotamine tartrate if administered early in the attack.

It is true that many patients will present a headache with some, but not all, of the above mentioned features of typical migraine headache. Indeed many of these patients will obtain satisfactory results by means of the same methods as those used in the treatment of typical migraine. However, the further from typical migraine the case may be, the less satisfactory migraine therapy will prove to be. Many of these atypical forms of headache will be on a psychogenic basis or may closely resemble histamine cephalalgia.[5] Many authors deny that there is any difference between histamine cephalalgia and migraine. However, the striking and dramatic appearance of the attacks of histamine cephalalgia and the response of the patients to appropriate treatment with histamine leave no doubt in our minds as to the difference in the two types of headache.

There are few clinical conditions about which more has been written, and for which so many different forms of therapy have been investigated, as migraine headache. Even at the present time new forms of treatment are being described at a rapid rate, and it is difficult to evaluate the reports. It will serve our purpose well, in discussing the treatment of migraine, to divorce the treatment of the acute attack from the treatment of the patient aimed at prevention of attacks. Although it is time consuming, and at times a harrowing experience, it is wise for the physician to observe his patient during a typical attack. In no other way is he able to understand what the patient is undergoing when he describes the attack. Many of the patients are so incapacitated during, and for several days after, an attack of migraine, that they have come to understand that once an attack is developing they must give themselves up entirely to it. They thus acquire an extreme sense of frustration in the belief that they can never obtain relief and must continue to suffer prolonged periods of agony at regular

5. Horton, B. T.: The Use of Histamine in the Treatment of Specific Types of Headaches, J. A. M. A. **116**:377 (Feb. 1) 1941.

intervals. It is a rare patient with migraine to whom proper individualized medical treatment during the attack of headache will not bring some measure of relief and shorten the duration of the attack and its after-effects. Once the patient realizes that something can be done for him, he is able to take a new lease on life and eventually to be the master of the situation, for he will know exactly what to do when an attack develops in order to overcome it quickly.

The intensity of attacks varies greatly in different patients. Some will suffer for only a few hours at the time of menstruation, whereas others may have severe attacks lasting several days at a time and recurring once or twice a week. In several of our patients migraine developed at two to four weeks intervals over a period of several years, necessitating hospitalization and intensive intravenous feedings for each attack. These patients are now brought to the office immediately on development of an attack; all food and medicine is withheld, and they are given glucose, saline solution and ergot parenterally as needed. In most instances this intensive early treatment aborts the attacks and circumvents hospitalization.

Treatment of the Individual Attack of Migraine: What is the patient to do when he awakens with a severe headache or when he feels one coming on during the day? As previously stated, the attack is usually preceded by a period of excitement and tension, and he will be in a state of high nervous tension when the headache develops. For this reason, and to prevent the build-up of an element of muscular tension, in addition to the actual migraine, he must learn to retire to a quiet, cool, dark place and recline if possible. He should be instructed in the proper administration of ergotamine tartrate (gynergen®) (0.25 to 0.5 mg. subcutaneously), dihydroergotamine (0.5 to 1 mg. subcutaneously),[6] the new "cafergot" (tablets, containing 1 mg. of ergotamine tartrate and 100 mg. caffeine) for oral use (2 tablets immediately and 1 every half-hour to a total of 4 to 6, as needed)[7] or a rectal suppository made up of a combination of ergotamine tartrate, 2 mg.; total levorotatory alkaloids of belladonna in form of malates (bellafoline®), 0.25 mg., and caffeine, 100 mg.[8] The wise patient will soon determine which of these is best for him in various circumstances and will learn to administer them himself. In this way he will not need to let the attack develop while waiting for a nurse or physician to administer the drug. In the average case proper therapy will bring about relief of the attack within one to two hours. An occasional patient will not respond to any of the drugs mentioned. In that case one is justified in trying one of the following procedures, although their exact value is yet to be determined in a large enough series of typical migraine attacks for adequate evaluation. It will be found that an occasional patient will respond well to one of these newer procedures, in which case he should be instructed in its proper use.

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6. Horton, B. T.; Peters, G. A., and Blumenthal, L. S.: A New Product in the Treatment of Migraine, Proc. Central Soc. Clin. Research **15**:91 (Nov. 6) 1942; A New Product in the Treatment of Migraine: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **20**:241 (July 11) 1945. Blumenthal, L. S.: Migraine Headache: Treatment of 51 Patients with Dihydroergotamine, M. Ann. District of Columbia **16**:10 (Jan.) 1947.

7. Horton, B. T.; Ryan, R., and Reynolds, J. L.: Clinical Observations on the Use of E. C. 110, A New Agent for the Treatment of Headache, Proc. Staff Meet., Mayo Clin. **23**:105 (March 3) 1948.

8. Supplied for clinical trial by Sandoz Chemical Works, Inc., New York.

1. Intravenous administration of nicotinic acid, 25 to 50 mg., sufficient to produce a definite flushing sensation.[9]

2. Inhalation of 100 per cent oxygen for several minutes.[10]

3. Oral or intramuscular injection of 6-methylamino-2-methylheptene (octin®) hydrochloride, 100 mg.,[11] to be repeated in one hour if needed and if no severe rise in blood pressure occurs.

4. Intravenous injection of 50 cc. of 50 per cent dextrose, useful in the later stages, when actual edema of the vessels is suspected.

5. Oral [12] or intravenous [13] administration of one of the antihistamine preparations.

6. Administration of sedative doses of barbiturates, or even narcotics, for a severe attack.

Prevention of Migraine: A proper understanding of his individual problem, including how and why his attacks occur, is the cornerstone to the long range treatment of migraine. In addition, any definite contributory causes found in the examination should be corrected. This will include proper thyroid,[14] estrogen or androgen supplementation when indicated. Foods and inhalants or other contacts known to precipitate attacks must be avoided. Use of antihistamine preparations is occasionally indicated in those cases in which an allergic relation is suspected.[12] Maintenance of optimum blood levels of potassium thiocyanate [15] (8 to 12 mg. per 100 cc.) in an occasional patient with or without hypertension may prove satisfactory if other therapy has failed. Parenteral and oral use of nicotinic acid in graduated doses has been reported to be of benefit.[9b] In our experience, it is a rare case of typical migraine that responds to this, although we do get satisfactory results with its use in myalgic or nervous tension headaches.

When the pain is predominantly related to the area supplied by a particular blood vessel, periarterial infiltration with procaine has been reported to give definite relief for varying lengths of time.[16] If relief is temporary, resection of the involved vessel might be indicated.[17]

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9. (*a*) Goldzieher, J. W., and Popkin, G. L.: Treatment of Headache with Intravenous Sodium Nicotinate, J. A. M. A. **131**:103 (May 11) 1946. (*b*) Atkinson, M.: Ménière's Syndrome and Migraine: Observations and Common Causal Relationship, Ann. Int. Med. **18**:797 (May) 1943.

10. Alvarez, W. C.: New Treatment for Migraine, Proc. Staff Meet., Mayo Clin. **14**:173 (March 15) 1939.

11. MacNeal, P. S., and Davis, D.: The Use of Methyl-Iso-Octenylamine in Migraine, Ann. Int. Med. **26**:526 (April) 1947.

12. Blumenthal, L. S., and Rosenberg, M. H.: Diphenhydramine Hydrochloride ("Benadryl Hydrochloride"): A Report on Its Use in 137 Patients, J. A. M. A. **135**:20 (Sept. 6) 1947.

13. Rosenberg, M. H., and Blumenthal, L. S.: The Clinical Uses of Intravenous Diphenhydramine Chloride: (Benadryl Hydrochloride), Am. J. M. Sc. **216**:158 (Aug.) 1948.

14. Fenichel, N. M.: Chronic Headache Due to Masked Hypothyroidism, Ann. Int. Med. **29**:456 (Sept.) 1948.

15. Hines, E. A., Jr., and Eaton, L. M.: Potassium Thiocyanate in the Treatment of Migraine: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **17**:254 (April) 1942; Treatment of Migraine with Potassium Thiocyanate, J. A. M. A. **121**:1307 (April 17) 1943.

16. Patzer, R.; Derbes, V. J., and Englehardt, H. T.: Periarterial Infiltration in Diagnosis and Treatment of Migraine: Experimental and Clinical Experiences with Eucupine and Procaine Hydrochloride, Arch. Surg. **50**:296 (June) 1945.

17. Watts, J.: Personal communication to the author.

There has been much discussion of late concerning the role of histamine in allergies [18] and in migraine.[19] Horton's early report on the use of histamine in the treatment of specific types of headache [20] showed that subcutaneous injections were not satisfactory in the treatment of migraine; however, he later reported [21] very good results with intravenous, followed by subcutaneous, injections. Butler and Thomas [19b] have obtained apparently excellent results with the prolonged intravenous administration of increasing doses of histamine. They give an intensive course of daily treatments at each of which 500 cc. of saline solution is given in which up to 2 mg. of histamine base is dissolved. The injection takes them three to eight hours to complete because of its tendency to precipitate a severe attack if allowed to flow too rapidly.

Our results with the one hour intravenous injections, given every other day, have proved fairly satisfactory with ambulatory patients. Of approximately 300 patients so treated, many are now working steadily after the initial course of treatments, extending over a period of one to two months. Many have maintained their improvement by continuing to receive an intravenous injection at intervals of seven to 10 days, while some have held it on maintenance subcutaneous therapy. Our over-all results with histamine used in the combination that seems best suited to each individual case show approximately 75 per cent improvement.

The solution used for intravenous administration in all cases is a specially prepared one,[22] each 100 cc. of which contains 0.55 mg. histamine diphosphate (equivalent to 0.2 mg. histamine base), and 0.90 Gm. sodium chloride. Each treatment is given as soon after breakfast or lunch as possible, and antacid tablets are chewed continuously during the injection in an effort to prevent any possible excess gastric acidity. The entire duration of the treatment is one hour; so it is possible for the patient to be treated in the office or clinic on an ambulatory basis and to return to work immediately. Comfortable beds with proper lighting are provided, as most patients prefer to read during the course of the injections. In order to make the procedure as attractive as possible, it is advisable to pay attention to small details, such as the use of a small (22) gage needle and infiltration of the skin overlying the vein with 2 per cent procaine hydrochloride solution. This will help

18. Farmer, L.: The Histamine Treatment of Allergic Diseases: I. Asthma and Vasomotor Rhinitis, J. Lab. & Clin. Med. **26**:802 (Feb.) 1941. Farmer, L., and Kaufman, R. E.: Histamine in the Treatment of Nasal Allergy (Perennial and Seasonal Allergic Rhinitis), Laryngoscope **52**:255 (April) 1942. Manrique, R. F.: Microdoses of Histamine in Allergy (Nonspecific Desensitization), Prensa méd. argent. **29**:1340 (Aug.) 1942. Johnson, G. D.: The Use of Histamine Compound in the Treatment of Infantile Eczema, J. South Carolina M. A. **42**:29 (Feb.) 1946. Ruszнyqák, S.: The Utilization of Histamine in Internal Medicine, Med. Klin. **33**:303 (Feb. 26) 1937.

19. (*a*) Blumenthal, L. S.: Current Histamine Therapy, M. Ann. District of Columbia **19**:191 (April) 1950. (*b*) Butler, S., and Thomas, W. A.: Intravenous Histamine in the Treatment of Migraine: Preliminary Report, J. A. M. A. **128**:173 (May 19) 1945. (*c*) Blumenthal.[18]

20. Horton, B. T.: The Use of Histamine in the Treatment of Specific Types of Headaches, J. A. M. A. **116**:377 (Feb. 1) 1941.

21. Macy, D., Jr., and Horton, B. T.: Treatment of Migraine with Histamine: Review of 144 Cases, J. A. M. A. **137**:1110 (July 24); **138**:224 (Sept. 18) 1948.

22. Generous supplies have been made available for use in the headache clinic at the George Washington University Hospital by Dr. Naurice Nesset, of the Baxter Laboratories, Morton Grove, Ill.

to alleviate the fears of any needle-shy patient. One of the most important details is to prevent the solution from running in too fast after venipuncture. The proper rate to begin each injection is approximately 5 to 10 drops per minute. The rate is then gradually increased to the point that will barely produce a sensation of mild flushing or fulness in the head. If this rate is exceeded, a typical attack of headache can easily be produced. After several treatments, most patients are able to receive it at a rate of 40 to 60 drops per minute. I have found that my results are equally satisfactory whether the patient receives 25 or 300 cc. of the solution, as long as he receives his particular tolerance dose for the one hour period.

The intravenous injections are given daily for four days and then every other day. The patient is instructed in the proper technique of subcutaneous injections [20] and is allowed to give these to himself at home as soon as he is satisfactorily "checked out" by the nurse. As soon as definite improvement is obtained, the intravenous injections are discontinued, and the subcutaneous "desensitization" is completed.

Histamine Cephalalgia (Horton's Headache).—Histamine cephalalgia was first reported, and its differentiation from migraine stressed, by Horton and associates in 1939.[23] At that time it was called erythromelalgia of the head. Characteristically this is a unilateral headache, which usually begins in males in the later decades of life, is of short duration, as it generally lasts less than an hour, commences and often terminates suddenly, tends to waken the patient at night one to two hours after he has gone to sleep and is frequently eased by his sitting up or standing erect. It is associated with profuse watering and congestion of the eye, rhinorrhea or stuffiness of the nostril, increased surface temperature and, often, swelling of the temporal vessels of the involved side of the head.

Pain is the outstanding complaint. It is constant, excruciating, burning and boring; it involves the eye, the temple, the neck and often the face. The pain seems to conform to the ramifications of the external carotid artery. Compression of the involved artery often affords temporary relief.

Although it is difficult to be sure that this condition is due to a release of histamine or a basic sensitivity to the drug, it has two definite clinical relations to histamine: 1. In most typical cases a subcutaneous injection of 0.1 to 1.2 mg. of histamine base will precipitate a typical attack within 50 minutes of injection. 2. In addition, gradually increasing subcutaneous doses of histamine, given twice daily, will usually bring about cessation of attacks in 10 to 30 days.[20]

The problem, then, will be to prevent recurrence of the headaches. This is accomplished by gradually decreasing the frequency of injections so that the tolerance dose is given once daily, then every other day, then twice a week. Eventually, one finds that the patient will be able to stop the drug entirely or will require an injection at a certain regular interval, such as once every seven to 14 days. Occasionally symptoms may recur after several months or a year or two, and repetition of the original "desensitization" regimen will usually again achieve satisfactory results.

23. Horton, B. T.; MacLean, A. R., and Craig, W. M.: A New Syndrome of Vascular Headache: Results of Treatment with Histamine; Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:257 (April 26) 1939.

Since September 1945, we have had the opportunity of treating 20 patients with histamine cephalalgia. Six of these patients had the onset of the headache before the age of 20, and five were females. We have modified our method of therapy from that of Horton's, as given above, by starting treatment of all patients with intravenous administration of histamine. We have found that in most patients notable relief of symptoms is obtained within several days of onset of therapy. In addition, 30 per cent of patients have required no subcutaneous therapy.

Hypertensive Headache.—The usual, or typical, headache of essential hypertension, like the migraine headache, is vascular in origin and has also been found to be associated with dilatation and stretching of the extracranial and, to a less degree, the dural arteries. The similarity between the two conditions is emphasized by the fact that migraine has been found to be five times as common in patients with hypertension as in a group of controls,[24] while a significant number of hypertensive patients had migraine headaches before the onset of their hypertension.

It is interesting to speculate on the possible influence of the rather similar types of personality makeup which are found in migraine and in hypertension, repressed and subconscious hostility being of psychodynamic importance in both.

Neither increased blood pressure[25] nor increased spinal fluid pressure[26] is directly correlated with the occurrence of headache in hypertensive persons, and drugs reducing blood pressure are not very successful in relieving the headache. The typical headache of hypertension is dull or throbbing, often predominantly frontal or frontotemporal and is present on awakening or awakens the patient in the early morning. Nausea and occasionally vomiting may be associated. It should be emphasized that neither these characteristics nor the mechanisms described apply to the severe cephalalgia associated with hypertensive encephalopathy. This form is often unilateral, may radiate to the back of the neck and may be associated with anorexia, vomiting, apathy or restlessness, amblyopia, convulsions, papilledema and extreme elevation of the blood pressure. Local edema of the brain resulting in traction on or displacement of the tributary veins to the great sinuses appears to be the mechanism involved in the headache of hypertensive encephalopathy.[27]

In the treatment of the typical hypertensive headache, ergotamine tartrate and caffeine have been found to be useful, as might be expected from the similarity in mechanism to the headache of migraine. Steiner[28] has recently reported good results with the use of 10 inch (25.4 cm.) blocks under the head of the patient's bed. Psychotherapeutic measures, varying from advice as to living habits to exploratory technique, are again an important element of a rounded treatment

24. Gardner, J. W.; Mountain, G. E., and Hines, E. A.: Relationship of Migraine to Hypertension and to Hypertension Headaches, Am. J. M. Sc. **200**:50 (July) 1940.

25. Sutherland, A. M., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of Mechanism of Headache in Migraine, Hypertension and Fever, Arch. Neurol. & Psychiat. **44**:929 (Nov.) 1940.

26. Shelburne, S. A.; Blain, D., and O'Hare, J. P.: The Spinal Fluid in Hypertension, J. Clin. Investigation **11**:489 (May) 1932.

27. Rosenberg, E. F.: Brain in Malignant Hypertension: Clinicopathologic Study, Arch. Int. Med. **65**:545 (March) 1940.

28. Steiner, S. A.: The "Typical" Headache of Essential Hypertension: Etiologic Considerations and Report of a New Form of Therapy, M. Ann. District of Columbia **14**:531 (Dec.) 1945.

regimen. Maintenance of a blood level of 8 to 12 mg. per 100 cc. of potassium thiocyanate often controls recurrent hypertensive headaches. Many patients can obtain relief of severe headaches after undergoing lumbar sympathectomy.

Temporal Arteritis.—Temporal arteritis is a rare disease in which unilateral or bilateral temporal headache is associated with fever, weakness, anorexia, loss of weight, anemia, mild leukocytosis and the presence of painful, tender areas over the scalp and along the course of the temporal vessels.[29] It appears to be a localized arteritis and periarteritis of unknown cause, with systemic evidences of infection. There is some resemblance to periarteritis nodosa, but temporal arteritis is self limited and localized and is a less serious condition. It usually occurs in older persons past 60 years of age. Shannon and Solomon [30] have reported a case in which bilateral temporal arteritis was associated with complete loss of vision. The mechanism of the pain is inflammatory irritation of the temporal arteries and periarterial tissues. Bowers [31] has advocated the use of large doses of thiamine chloride in the treatment, but resection of a small segment of the involved artery is usually necessary.

The fact that the pain of temporal arteritis resembles that of other vascular types of headaches led us [32] to treat a recent patient with intravenous injection of histamine. The patient's pain was abating when therapy was started and was completely gone after two days of treatment. However, daily injections were continued for 33 days in an attempt to study its effect on the patient's blindness. Although objective evidence of improvement was lacking, the pathological changes did not progress as far in this case as is usual. A recent report by Horton [3b] describes the use of histamine in one of his patients, in whom it was rather successful in controlling symptoms. This patient did not have retinal involvement; therefore the author could not evaluate the effect of histamine on the blindness of temporal arteritis.

Post-Traumatic Syndrome.—Vasodilating headache is a prominent feature of the post-traumatic cerebral syndrome. The exact mechanism of production of this disorder is not entirely clear, and it is generally agreed [1a] that in most cases a large functional element is at work. Friedman and Brenner [33] were able to reproduce in 13 of 20 patients the headache of which these patients complained by injecting 0.1 mg. of histamine base (0.275 mg. histamine diphosphate) intravenously, and brought up the question of the use of histamine in the therapy of this condition. Horton [3b] stated that he has been agreeably surprised with the results obtained with intravenous injection of histamine.

We have had the opportunity of treating five patients with the typical post-traumatic cerebral syndrome with daily intravenous administration of histamine, as described above. Two of these patients had sustained their head injuries three years prior to treatment; one had received the injury five months prior to treatment, and

29. Horton, B. T.; Magath, T. B., and Brown, G. E.: Arteritis of Temporal Vessels: Previously Undescribed Form, Arch. Int. Med. **53**:400 (March) 1934.

30. Shannon, E. W., and Solomon, J.: Bilateral Temporal Arteritis with Complete Loss of Vision, J. A. M. A. **127**:647 (March 17) 1945.

31. Bowers, J. M.: Arteritis of Temporal Vessels: Report of a Case, Arch. Int. Med. **66**:384 (Aug.) 1940.

32. Meade, D. K.; Blumenthal, L. S., and Holmes, D. B.: Temporal Arteritis: Report of a Case Treated with Intravenous Histamine, South. M. J. **43**:40 (Jan.) 1950.

33. Friedman, A. P., and Brenner, C.: Post-Traumatic and Histamine Headache, Arch. Neurol. & Psychiat. **52**:126 (Aug.) 1944.

in two therapy was begun within two weeks of the accident. Although headache could always be produced by rapid intravenous injection of histamine, these patients were able to tolerate the injections at a much more rapid rate than could patients with migraine or histamine cephalalgia. The first observation volunteered during treatment was an apparent striking clearing of the sensorium, as though a cloud had been lifted off the head. Three patients noticed definite relief of symptoms during the first week of therapy, whereas the improvement in the other two was gradual, but progressive, over the course of several months. The average number of intravenous injections was 15. Subcutaneous therapy was not needed in any of these cases.

SUMMARY

The several conditions discussed include the majority of cases of headache seen in the practice of internal medicine. Some cases will not fall into any of the above mentioned groups, but the attempt to classify each case properly will simplify and improve the effectiveness of the medical management. The correct diagnosis allows the physician to approach the problem of headache with more optimism, and this attitude and approach are generally rewarded with encouraging results.

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AN ASSESSMENT OF THERAPY IN PARKINSON'S DISEASE

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SINCE 1817, when James Parkinson [1] recognized the entity of paralysis agitans among the heterogeneous collection of tremors and paralyses, the most persistent attempts have been made to treat this disease. It is instructive to review some of the methods used and the claims that have been made for them.

Parkinson himself suggested that blood be taken from the upper part of the neck, that vesications be applied to the same part and a purulent discharge obtained by use of the Sabine liniment. If that should fail, an issue should be made, and kept open, beside the vertebral column. He reasoned, on ingenious theoretical grounds, that improvement should result. Before very long this method had fallen into disrepute, and we read of Elliston [2] giving carbonate of iron and of Brown-Séquard [2] giving barium chloride. Both reported cures, as well as some remissions and some failures. Then Trousseau [2] reported strychnine as being decidedly beneficial. A little later Charcot [2] himself wrote that carbonate of iron and barium chloride were, in his opinion, useless. He, for his part, used belladonna and scopolamine, with some improvement in the symptoms. Charcot,[2] too, thought that some of his patients were benefited by riding on horseback. Consequently, he had constructed a *fauteil trepidant*, on which he made his patients sit and shake for stated periods. A pupil of his, Gloreux, was so impressed with this idea that he prescribed for his patients a two hour ride each day on as bumpy a conveyance as was possible. At the turn of the century Gowers [3] expressed the opinion that scopolamine and belladonna were of little value and that most good could be obtained with arsenic or Indian hemp.

Hormones of almost every kind have been used enthusiastically at one time or another. Berkely,[4] for instance, gave parathyroid extract to 65 patients, with

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1. Parkinson, J.: An Essay on the Shaking Palsy, London, Whittingham and Rowland, 1817.

2. Charcot, J. M.: Leçons sur les maladies du systeme nerveux, Progr. méd. **2**:147-272, 1874.

3. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston's Son & Co., 1903.

4. White, W. A., and Jelliffe, S. E.: The Modern Treatment of Nervous and Mental Diseases, Philadelphia, Lea & Febiger, 1913, vol. 2, chap. 15.

improvement in many and apparent cure in some. Shortly afterward, Roussy,[4] who thought that the parathyroids were overactive in patients with paralysis agitans, applied radium to the neck and reported improvement in three cases.

Oppenheim[4] believed that his patients would improve in wooded and low mountain areas. Nolda[4] thought that high mountains were far better and sent his patients to such places as San Moritz.

In 1926 Ivan Raeff, a plant collector in the Bulgarian village of Chipka, became famous for his Bulgarian belladonna cure.[5] Minute instructions were given on the preparation and administration of the drug. It had to be taken once in the 24 hours "after the first sleep." Various pills were given in addition, which proved, on analysis, to consist of charcoal, bread dough, sawdust, nutmeg and calamus root. A daily routine was prescribed which included bathing in water warmed by the sun and sleeping only on the right side. In all parts of the world the successes claimed were phenomenal. Now, however, most people would agree that there is little, if any, difference between belladonna root grown in Bulgaria and belladonna root grown elsewhere and that there is no need for the other, somewhat mystical pills and associated ritual.

How is it that one is able to find such glaring discrepancies? One cannot question the integrity of the observers. Names such as Charcot, Oppenheim, Gowers and Brown-Séquard are among the most revered in neurology. Furthermore, differences of opinions such as these are by no means restricted to the reports in the older literature. Today we find Sigwald[6] reporting that diethazine hydrochloride (diparcol®) gave very good results in 20 per cent, good results in an additional 33 per cent, fair results in 24 per cent and slight to no effect in 23 per cent. This represents a successful score of 77 per cent, a very satisfactory figure. On the other hand, Palmer[7] found this drug favorable in only 30 per cent. Likewise, Schwab and Leigh,[8] in 1949, found caramiphen (panparnit®) hydrochloride useful in 72 per cent of their patients, while Sciarra and associates[9] found it less effective than the belladonna alkaloids (less than 30 per cent).

The answer is not difficult to find. In the first place, the improvement to be expected from even the best drugs available is comparatively slight. When their results are compared with those of insulin in diabetes or of neostigmine in myasthenia gravis, their limitations are obvious. If properly used, insulin can return a diabetic patient to almost normal health—a 95 per cent rehabilitation (fig. 1). The same is true of neostigmine, although the effect lasts only a short time. These drugs are so superior to any others that they are in effect the only ones used for control of these diseases. The mere multiplicity of therapeutic measures in Parkinson's disease is an indication of the inefficiency of each. The patient with this

5. Vollmer, H.: The Bulgarian Treatment of Post-Encephalitic Parkinsonism, J. Mt. Sinai Hosp. **6**:93, 1939.

6. Sigwald, J.; Grossiord, A.; Durel, P., and Dumont, G.: Clinical Applications of N-Diethylaminoethyl-Phenothiazine (2987 R. P.) in the Treatment of Parkinsonian States, Rev. Neurol. **79**:683-687, 1947.

7. Palmer, H., and Black, H.: Diparcol Therapy for Parkinsonism, New Zealand M. J. **48**:487-490, 1949.

8. Schwab, R. S., and Leigh, D.: Panparnit in the Treatment of Parkinson's Disease, J. A. M. A. **139**:629-634 (March 5) 1949.

9. Sciarra, D.; Carter, S., and Merritt, H. H.: Caramiphen Hydrochloride (Panparnit) in the Treatment of Diseases of the Basal Ganglions, J. A. M. A. **141**:1226-1229 (Dec. 24) 1949.

disease is not nearly completely rehabilitated—an improvement of 25 per cent toward normality is about the best that can be expected. When such small improvements are to be assessed, very small differences in the effectiveness of each drug become important. Nevertheless, this 25 per cent improvement can be vital to the patient. It may make the difference, for example, between his relying on some one else to help him out of bed and being able to do it himself. A tremendous advance in terms of social rehabilitation and the encouragement that even a slight change for the better gives will do the morale of the patient a great deal of good.

The second reason is the difficulty of assessing improvement in this disease. Parkinsonism is subject to wide, and often rapid, variations in severity, depending in part on the state of mind of the patient. If he is relaxed and drowsy, the tremor and rigidity are minimal. If he is tense and excited, they are severe. It is impossible to regulate the patient so that the tremor and rigidity at a given time on one day are directly comparable to the tremor and rigidity on a different day. A good breakfast and a rise in the stock market might make him feel happier and relaxed,

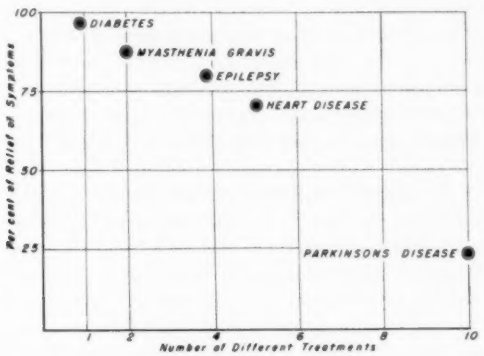

Fig. 1.—Diagrammatic relation, showing the low percentage of relief of symptoms in Parkinson's disease as contrasted with a high percentage of relief of symptoms in four other diseases. There is a direct relationship of the number of treatments to the success of treatment, as shown in the graph.

with a reduction of the tremor, while burnt toast and an unfavorable election victory might make him unhappy and tense, with worsening of the tremor. Furthermore, the change in the state of the disease due to an emotional cause may not be temporary only. We have found permanent changes for the worse in some patients due, apparently entirely, to this cause.[10] Some investigators believe that a sudden change in the severity of the disease is always due to an external cause.

In 1949 [8] Leigh and one of us (R. S. S.) stated that one of the attributes of successful drug treatment of any condition is that the results must not depend on the individual aptitude of any physician. When the drug is administered by any doctor in any part of the world, it should produce uniformly successful results. If it is given by a nurse or a lay person, or even if taken by the patient on his own

10. Schwab, R. S.; Prichard, J. S., and Tillmann, W. T.: The Relationship of Stress and Personality Type in Parkinson's Disease, Psychosom. Med., to be published.

initiative, the same benefit should be obtained. This is certainly true of insulin, acetylsalicylic acid, morphine, sulfonamide drugs and many compounds whose success has been established through the years. With these drugs the effect is clear and definite, and over 90 per cent of the symptoms are relieved.

In cases of Parkinson's disease, however, the average relief of symptoms, as previously stated, is between 20 and 25 per cent. No drug known today returns the patient to a normal state of health or relieves the symptoms to the degree that insulin does in diabetes. Furthermore, stresses in the environment of a patient with Parkinson's disease will cause a clearcut exacerbation in the symptoms.[10] The ambition of an investigator in prescribing a therapeutic regimen is to free himself entirely from the obvious criticism that he is overenthusiastic or that his friendly personality plays a major part in the success attributed to the medication he uses. This is particularly true of skeptical workers who devise a number of safeguards and checks against being involved unwittingly as a source of error in the assessment of the therapy. The extreme of such protection in being overscientific involves the substitution of the patient by an animal, in which situation personal contact can be entirely avoided. The obvious extreme of carelessness is dependence entirely on the mail reports of patients on how they are getting along. The more one treats patients like guinea pigs, the more one eliminates from the investigation the normal doctor-patient relationship, interest in the patient's well-being and the friendly and supportive advice and help that is the essence of a good physician. This creates in the patient resentment, hostility and identification of himself as an experimental animal.

In the case of Parkinson's disease excessive scientific detachment in a therapeutic regimen will build up enough disappointment and resentment in the patient to produce exacerbations and symptoms that may well neutralize any benefit that the therapy can achieve. It is essential, in assessing the effects of therapy in this disease, to maintain the usual level of friendly, supportive patient-doctor relationship. On this level as a base line the increments of therapeutic success due to the drugs should be assessed. It is ridiculous for those who are unaware of the importance of this factor to attribute the success of one investigator with a compound to overenthusiasm or hidden factors and neglect the same negative values deliberately left out of his own relationship in an effort to be ultrascientific.

It is certain that the discrepancies in the present literature and in the literature of the past among reputable investigators lies largely in this sphere of misunderstanding. When a physician fails to match the results of another, it is wiser to review minutely the technique of the latter rather than to jump to illogical conclusions. At least it is better manners to do so, and this may well lead to better understanding of the numerous techniques that are available.

Since the objective and subjective improvement produced in a case of Parkinson's disease by the medicines that are available at present is usually no more than 10 to 25 per cent of remission toward a 100 per cent state of good health (the physical state of the patient before the onset of Parkinson's disease), comparative assessment of different therapies is hazardous. For example, if a patient is improved approximately 15 per cent with stramonium during the course of a year, and treatment is then changed to one of the new compounds, such as trihexyphenidyl (artane [8]) or caramiphen, which produce in favorable cases improvement to perhaps 20 or 25 per cent, there is only a differential of 5 to 10 per cent to guide one in one's

estimation of relative efficiency. As previously shown, the variability from day to day, and week to week, is a factor. It is not easy to be certain that a 10 per cent change is due entirely to the new medication in patients who are subject to sudden and unexpected changes due to situations in their external environment.

EVALUATION TESTS

For the past five years we have endeavored to devise tests and techniques that are objective and simple and that will allow us to be more accurate in the determination of relative efficiency of drugs. The first source of error in the estimation of improvement in any patient with chronic disease is the psychological stimulation or support given by a physician who is interested in, and perhaps enthusiastic about, new therapeutic methods. We are keenly aware of this source of error and have endeavored to counteract it by having a large group of patients followed for a long time, and then have a number of different clinical observers take part in the investigation. As an additional safeguard against misinterpretation of data due to overenthusiasm on the part of the physicians, the laboratory tests which show the state of improvement were made by technical co-workers, who were not aware of the type of medication being used and who had a minimal personal interest in the changes of the patient from visit to visit.

Unless these laboratory tests are numerous and are subject to the same results when different technicians employ them, they are not accurate enough. A large number of objective tests have been used in the past five years, many of which were discarded because they were complicated, cumbersome or unreliable. The tests that have been retained indicate improvement on the part of the patient that corresponds with betterment in his clinical state. They are simple enough to perform, do not tax the patient or the technicians unduly and give the same results when done by different persons. They are listed in order of their apparent clinical value, as follows:

1. *Dynamometric Reading.*—A simple hand dynamometer is used to test the grip in each hand. Patients with hemi-Parkinsonism have a normal grip on the uninvolved side and a rather striking loss of strength on the involved side. The results are read in kilograms and are practically constant in patients from month to month.

2. *Finger-Thumb Proximation Rate.*—The proximation of the index finger and the thumb and their opening again as fast as the person can do this is an excellent index of muscle utilization. This is usually done for a period of 10 seconds, and the technician uses a stopwatch to insure accuracy. The rate was checked by electrical methods with contacts on the thumb and finger and an automatic count. The patient performs the test with each hand. The rates for patients with Parkinson's disease are much slower than those for normal persons. For example, a normal person can obtain a finger-thumb rate of approximately 5 per second, whereas a person with Parkinson's disease usually is unable to go higher than 3 to 4 per second, even with considerable benefit of drug therapy. Severely incapacitated patients with Parkinson's disease may have a rate as slow as 1 per second. The rate from month to month is remarkably constant in patients wth relatively fixed symptoms. Exacerbations of the disease or remissions in symptoms are accompanied with a corresponding slowing or increase in the finger-thumb rate.

3. *Circle Drawing.*—The patient, sitting in a comfortable position, is given a pad of paper and instructed to draw with a pencil 10 circles of 6 cm. diameter as fast as he can, using first the right hand and then the left hand. This gives an objective test, as well as a permanent record of the patient's performance. Tremor is indicated in the drawing of the circle by irregularities in the lines. The total elapsed time required to draw the 10 circles is measured by a stopwatch.

4. *Chair Test.*—A simple test in muscle control and coordination is the determination of how long it takes the patient to get out of a chair and assume the erect posture. In order that this test should be kept as accurate as possible, the same chair was used by the patient on each visit. A normal person can get out of a chair of this sort in less than one-half second. Patients with Parkinson's disease take from three-fourths to three seconds to attain this, and some severely incapacitated patients are unable to get out of the chair at all. In order to measure the time accurately, it is necessary to have a stopwatch that reads in fractions of a second. A stopwatch that reads in tenths of a second was used.

5. *Handwriting Test.*—On every examination the patient writes his name, and the appearance of the handwriting is an indication of the clinical state of the patient being tested.

6. *Gait.*—Since the gait is frequently involved in Parkinson's disease, the measurement of the time it takes the subject to walk briskly along a measured 10 meter course is obtained. A stopwatch is used for this test. The normal person usually can walk this 10 meter course in approximately five seconds, whereas patients with Parkinson's disease will take as long as eight to 15 seconds to walk the same distance. This test also follows rather well the clinical state of the patient from time to time.

7. *Electromyogram.*—The electromyogram is an objective measurement of the degree of involvement of Parkinson's disease. If electrodes are placed over the flexor or extensor muscles of the forearm, the degree of electromyographic discharge produced by the tremor is roughly proportional to the amount of tremor. On the other hand, a patient who has only rigidity and little tremor also produces a continuous spontaneous electrical discharge in the electromyogram, which appears different from that due to tremor alone. Since the amount of tremor in a patient with Parkinson's disease varies from minute to minute and is subject to various effects of tension and relaxation, this test is quantitated in the following manner:

The patient is seated as comfortably as possible by the technician in a quiet room to which he is accustomed. The electrodes are attached, and all arrangements are made for the recording before the test is actually taken. The run which we use is five minutes in length, and there is available with the equipment an integrating voltmeter, which totals the amounts of electrical discharge during this period. This is a check against the inspection of the record and any visual assessment of the amount of discharge in the electromyogram. For example, a normal person who sits in a chair in this way may have no electrical discharge whatever during the five minute period. A patient with very mild involvement with Parkinson's disease will have periods when there is no electrical activity at all and other periods during the five minute time when there is some activity. Severely involved Parkinsonian patients show continuous activity for the whole period. As stated before, this test does not differentiate between the amount of tremor and the amount of rigidity, but it does give a reasonably objective measurement of the amount of extrapyramidal involvement.

8. *Neurological Assessment.*—The remaining three objective tests in use are done by one of the medical observers and consist of the usual assessment of cogwheel rigidity, tremor in each arm and each leg and free swing.

Assessment of Rigidity: This test is usually made by passive flexion and extension of the limbs, the patient being instructed to be as relaxed as possible. In this series of observations, 0, 1+, 2+, 3+ and 4+ are used as indexes of various degrees of involvement. The normal person would show a rating of 0 for all the muscles examined, and a severely involved Parkinsonian patient with bilateral symptoms would show rigidity as high as 3+ and 4+ in all limbs.

Assessment of Tremor: This observation is simply the recording of the medical observer's estimate of the amount of tremor that the patient shows during the visit and during the neurological examination. This is assessed in the same way as the rigidity.

Free Swing: Wartenburg[11] has suggested the test to be described as a reliable method of indicating involvement of the extrapyramidal system. It consists of two parts. In the first part, the patient stands in as normal a position as he can, and the observer places a hand on each shoulder and as rapidly as possible rotates the shoulder back and forth a few times. The normal subject performing such a maneuver shows a free swinging movement of each arm

11. Wartenburg, R.: Pendulousness of the Legs as a Diagnostic Test, Neurology **1**:18-24, 1951.

which reaches in many patients an angle of 45 degrees. In cases of Parkinson's disease with unilateral involvement there is a normal swing on one side and no swing at all on the involved side. In mild cases there is a reduced swing and in severe cases no swing even with quite violent rotation.

The second part involves the observation of the amount of free swing at the knee. The patient sits on a table so that his knees can swing back and forth freely. The observer sits in front of him and tells the patient to relax as much as possible, then pulls out both feet to approximately a 45 degree angle and lets them go. In a normal person the knee will swing back

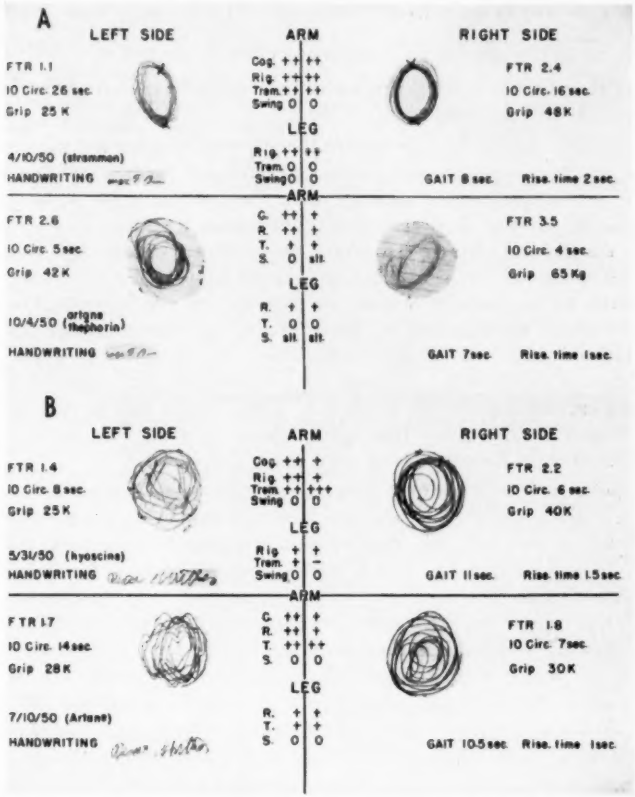

Fig. 2.—Two examples of how the objective data obtained from the various tests used appear in our records. *A* shows the favorable change that was produced by a drug, and *B*, a failure to produce improvement. The electromyographic clicks were omitted, owing to crowding. For *A* (a man aged 75) they were 147 before and 49 after drug therapy, and for *B* (a woman aged 65), 210 before and 225 after therapy.

and forth four or five times, gradually coming to rest. In a patient with Parkinson's disease, a rigid stopping of the involved leg will be observed, there being no more than one actual swing in most cases (fig. 2).

Other Tests.—In addition to the 10 objective tests which have been mentioned above, each patient is questioned about his mood; his subjective feelings and his performance of ordinary acts, such as shaving, feeding himself, dressing and walking up and down stairs; his performance

of work, and his participation in hobbies and all the minor and major events ordinarily encountered in everyday living. The patient is instructed to report a percentage of either improvement or lack of improvement after medication based on the degree of return to his preillness level. Even though he may feel remarkably improved and at first instance report 100 per cent improvement, if it is explained to him that 100 per cent improvement would be complete disappearance of all symptoms, a rather reasonable percentage estimate was usually given. This estimate is 10, 15, 20 or 25 per cent. The patient's relatives, in particular the mate, is also asked to give an estimate in the same manner. These estimates, along with the general appearance of the patient and the report of his activities at home, are loosely integrated into an estimate on the part of the examining physician as to the degree of improvement or failure of the drugs tested.

TREATMENT

During the past five years patients with paralysis agitans were given four types of treatment, as well as combinations of them.

Physical Therapy.—Either the routine therapy with massage and passive motion was given, or intensive progressive resistance exercises of the involved muscles were carried out in a special group of patients, under the direction of Dr. T. L. DeLorme. As concerns the effect of physical therapy of the routine type, namely, referral of the patient to the physical therapy department two or three times a week for massage and passive motion, or having a masseur come to the patient's home two or three times a week for the same treatment, we have formed the following impression: During the actual massage and passive exercises the patient almost always felt better. He was more relaxed and comfortable. As soon as the patient left the physical therapy department, his symptoms returned, and the benefit of the treatment lasted only an hour or two at the very most. There was no evidence in this type of physical therapy of any true benefit, change in symptoms, improvement in signs or alteration in the progress or state of the disease.

The special approach through progressive resistance exercises is a separate project, in which a specific weakness or stiffness in one muscle group, for example, in the left leg, or even both legs, rather than a generalized involvement, is the chief disability. These patients are seen in consultation with Dr. T. L. DeLorme and are taken into this project only if they are willing to come in for two to three hours' treatment, four times a week, for two to three months. The other forms of therapy, usually medication, which the patients have been receiving are kept exactly the same throughout this period of observation. Careful assessment is made each week as to changes in signs and in the patient's ability to perform his usual tasks at home and at work. At the end of the project the treatment is stopped for a period of at least a month to see whether any improvement attained has regressed.

In a preliminary group of five patients receiving this type of treatment, three have greatly improved in their strength and muscle function and in the ability to use these muscles in normal activities, such as walking and climbing stairs. There has also been a favorable improvement in mood. However, there is no alteration in the objective signs, such as tremor or rigidity or loss of associated movements. One patient in this group continued for six weeks and then reverted suddenly to the previous level after he had been badly shaken up in an automobile accident. This stress was sufficient to make the period of treatment following the accident (one month) ineffective. The fifth patient showed no improvement in any form, and the treatment was discontinued at the end of a month. Details of this project will be published in a separate communication.

Psychotherapy.—This consisted in a planned regular series of interviews with a group of unselected patients over a period of two to three months under the direction of Dr. W. T. Tillmann. This project was completed during 1949. Thirty unselected patients (the only selection was that the patient agreed to come in regularly for psychotherapy—some patients were busy and indifferent to this type of investigation and refused to come) were interviewed by Dr. Tillmann, and psychotherapy was instituted around the material brought out in these interviews over a period of three, and in some cases four, months. During this period medical treatment with drugs was maintained and unchanged, following the lines of previous therapy. Details of this investigation are to be published.[10] During the actual time that frequent psychotherapeutic interviews were taking place, two thirds of the patients reported a subjective improvement in morale, mood and a general feeling of well-being. There was no objective evidence of improvement in tremor or rigidity, movement rates or ability to perform tasks in their daily lives. In the entire group of two thirds who showed subjective improvement, this disappeared when the psychotherapeutic interviews ended. In one third of the patients taking this type of treatment there was no improvement during the interviews, and the patients continued to keep the appointments because of loyalty to the investigation, in the hope that something favorable might turn up later.

Surgical Treatment.—In selected patients, usually those with unilateral symptoms, signs or involvement, neurosurgical procedures were performed, on the opposite side, such as ablation of areas 6 and 9 (Klemme technique), cutting of the extrapyramidal fibers of the cerebral peduncle and unilateral leukotomy.

In the period from 1941 to 1943, James White followed the technique reported by Klemme in removing cortex to the depth of 1 cm. in areas 6 and 9 on the side opposite that most involved with Parkinson's disease. In one patient, a 21 year old musician, the tremor and stiffness in the left arm nearly disappeared after the operation. This was verified by clinical follow-up examination and electromyographic studies for a 10 year period. On the other hand, focal Jacksonian epilepsy developed, which was partially controlled by large amounts of diphenylhydantoin and phenobarbital. The patient had a moderate change in personality, so that he gave up his musical interests and became a filling station operator. He no longer worried over financial difficulties or his appearance, and he reported that subjectively he was much happier, and that he was carefree and contented. All the other patients who had this type of operation were not benefited at all.

Two patients were operated on according to the technique of Wyke.[12] Neither of these was helped in the slightest, and, as reported in the article, seven other patients, operated on elsewhere, were also not benefited.

In one patient a section of the extrapyramidal fibers in the peduncle was done, with complete relief of tremor and rigidity on the opposite side. There was also disappearance of the intolerable pain that had plagued her.

Three patients had unilateral leukotomy for pain and mental depression associated with Parkinson's disease. One was not improved, and two were greatly improved, with relief of the pain and depression. There was no change in the Parkinson's disease.

12. Cobb, S.; Pool, L. J.; Scarff, J.; Schwab, R. S.; Walker, A. E., and White, J. C.: Section of U Fibers of Motor Cortex in Cases of Paralysis Agitans (Parkinson's Disease): Report of 9 Cases, Arch. Neurol. & Psychiat. **64**:57-59 (July) 1950.

Drug Therapy.—During the past five years we have investigated 17 drugs, usually using each drug by itself. Sometimes two or more drugs have been combined. The following drugs have been tested:

Belladonna Group

1. Atropine sulfate
2. Belladonna alkaloid
3. Scopolamine hydrobromide
4. Stramonium

New Synthetic Antispasmodics

1. Trihexyphenidyl (artane®; 3-[1-piperidyl]-1-phenyl-1-cyclohexyl-1-propanol hydrochloride)
2. Diethazine hydrochloride (diparcol®; diethylaminoethyl-thiodiphenylamine)
3. Caramiphen hydrochloride (panparnit®)

Antihistaminics

1. Diphenhydramine (benadryl®)
2. Dimenhydrinate (dramamine®)
3. Pyrilamine maleate (neo-antergan®)
4. Phenergan (promethazine)
5. Synopen (dimethylaminoethyl chlorbenzyl-aminopyridin)
6. Chlorothen citrate (tagathen®)
7. Phenindamine (thephorin®)

Miscellaneous Group

1. Dexedrine sulfate® (d-amphetamine sulfate)
2. Neostigmine
3. Mephenesin (tolserol®)

The following drugs from the foregoing list were tested in both tablet and capsule form and were also made into elixirs.

1. Trihexyphenidyl
2. Diphenhydramine
3. Diethazine
4. Dimenhydrinate
5. Caramiphen
6. Phenergan
7. Synopen
8. Chlorothen citrate
9. Phenindamine

With all patients treatment was first tried with a single drug. If this failed to be beneficial, another single drug was tried. When some form of success was obtained, a period of two to three weeks of use of this single drug was allowed to elapse, and then various combinations of the drug were tried. In some cases as many as eight different drugs were tried with failure before some degree of success was obtained. In others as many as 10 combinations were tried before a successful one was found. The average number of trials before some form of success was obtained was two, and the combinations tried averaged three attempts.

We also tried the elixirs to see whether they would be better tolerated or more effective than the capsule or tablet form.

TABLE 1.—*Details of Technique in Obtaining the Therapeutic Index of Ten Drugs Used in Parkinson's Disease as It Was Worked Out in 1949 by W. T. Tillmann*

Drug	1 Best Alone × 4 +	2 Good Alone × 2 +	3 Good in Combination × 1 +	4 Toxic Side Effects × 4 −	5 Indifferent (No Effect) × 2 −	127 Cases Index of Therapy $+\left\lvert\frac{1+2+3}{4+5}\right.$
1 Artane®	33	15	36	10	12	3.1
2 Panparnit®	70	15	54	30	8	2.8
3 Benadryl®	3	21	45	8	8	2.0
4 Stramonium	9	21	12	18	31	0.8
5 Thephorin®	0	2	10	3	5	0.6
6 Diparcol®	2	5	6	11	4	0.5
7 Scopolamine or belladonna.	6	14	12	43	66	0.3
8 Dramamine®	0	0	3	0	8	0.2
9 Myanesin®	0	0	2	0	8	0.1
10 Amphetamine	2	11	18	18	22	0.4

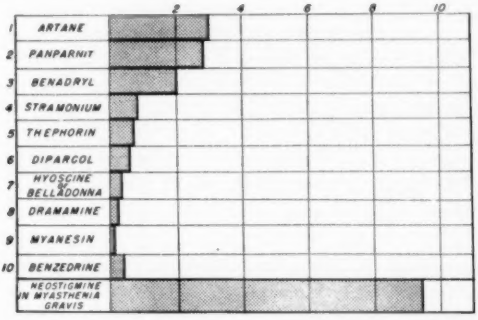

Fig. 3.—The comparative efficiency of 10 drugs used in the treatment of Parkinson's disease, the therapeutic index being used as a comparative figure. These are contrasted with the effect of neostigmine in myasthenia gravis. This chart was prepared by W. T. Tillmann in 1949.

There was need of some form of simple comparison of these drugs in order to give them any sort of relative value. Therefore the following scheme, called the therapeutic index, was used. This consisted in including the number of patients most favorably affected by a single drug into one group for each drug used. A second group for each drug was obtained from the patients showing the second best effect with the single drug. A third group, in which the drug was used successfully in combination with other drugs, was also formed. The number in each of the three groups was then multiplied by the following factors: the first group, by 4; the second group, by 2, and the third group, by 1. These three groups constituted the assets of any drug which we were testing. The deficits of the drug were determined by the number of patients who reported no effect, i. e., an indifferent result of the drug, and the number of patients who had side effects sufficient to cause the drug to be discontinued. The first group was multiplied by 2; the second group, by 4. The index was obtained by the simple ratio of the sum of the assets over that of the deficits (table 1). This ratio proved to be over unity for a

number of drugs and less than unity for those drugs that were less effective. Two sets of therapeutic indexes were obtained. One was taken in August 1949, when Dr. W. T. Tillmann reviewed the records of 125 patients. The second therapeutic index was obtained in May 1950, when one of us (J. S. P.) went over the records of 100 patients. The two indexes are not very different in their absolute values and are remarkably similar in their relative positions. The technique was checked without using the index by a simple percentage grouping of the successes and failures. The summary of the therapeutic index is shown in figure 3 and table 2. The first therapeutic index has already been reported elsewhere.[13]

COMMENT

The general impression from the assessment of the effectiveness of the above mentioned drugs as shown by the therapeutic index and by examination of protocols in the case histories, is that there is no one drug of choice. All drugs mentioned in the first two thirds of the list as they appear in the therapeutic index should be

TABLE 2.—*Comparative Effectiveness of Ten Drugs Used in Parkinson's Disease, the Therapeutic Index Being Used, As Well As a Percentage Relationship* *

	Drug	Number of Cases	% Favorable Effects	Therapeutic Index
1	Artane®	75	78	8.4
2	Panparnit®	87	64	3.5
3	Benadryl®	72	61	2.1
4	Stramonium	58	52	2.2
5	Scopolamine	92	46	1.9
6	Phenergan	14	43	1.0
7	Belladonna alkaloid	27	37	1.3
8	Thephorin®	41	32	0.6
9	Amphetamine	36	31	0.5
10	Diparcol®	25	24	0.5

* This chart was prepared by one of us (J. S. P.) in 1950. Note the similarity of the relationship to figure 2.

available to any physician for treatment of patients with Parkinson's disease. The variability from patient to patient, and from year to year in any one patient, as well as the changes due to stress, progression of the disease and a variety of other complicating factors, makes unwarranted any final conclusions that one drug is better than another. One of the easiest drugs to administer, with a minimal of side effects and a good general response, is trihexyphenidyl (artane®). Another favorable one is caramiphen (panparnit®), although this drug requires much more careful administration and observation against side effects in order that it may be tolerated by the patient. Caramiphen is useful in the treatment of Parkinson's disease, but it must be given in small doses for a time with a small increment each day or so, and then decreased to smaller doses as soon as side effects appear. If the physician is willing and able to supervise his patient closely, see him frequently and be in close contact with him, caramiphen in some cases produces more dramatic results than trihexyphenidyl. The only explanation of the failure of other investigators to find this drug of value is in the unwillingness on their part or the part of their patients to fulfil the criteria of careful and individual regulation.

13. Schwab, R. S.: The Treatment of Parkinson's Disease, Postgrad. Med. **9**:53-55, 1951.

Diphenhydramine (benadryl®) is the only antihistamine preparation effective alone in the treatment of this disease. Chlorothen citrate (tagathen®), synopen and pyrilamine maleate (neo-antergan®) have been failures. Phenergan has proved useful in a few patients. Phenindamine (thephorin®) when in combination with trihexyphenidyl has produced very gratifying results in many patients. It is the best combination we have. In a few patients diethazine hydrochloride (diparcol®) has been superior to any other drug tried, but the large majority of patients who took this drug had to stop its use because of the unfavorable side effects. This gives it a very low score in our therapeutic index. We were not able to duplicate the high degree of success reported by Sigwald and associates [6] in spite of repeated trials.

Some patients require a change in medication after a lapse of time, which may vary from three weeks to two years. Other patients continue on treatment with the same drug for three to four years with apparently no development of tolerance or change in the beneficial effects. Some patients actually fare better on a continuation of the same medication indefinitely than when treatments are changed regularly. There is so far no evidence for any general law that patients with Parkinson's disease do better with frequent changes in their treatment. The reason for benefit after many changes of treatment is that the treatment discontinued has not been the correct one. With over 65 per cent of patients, when a single drug or a satisfactory mixture has been found producing subjective and objective benefit, the medication can be continued indefinitely. The remainder, 35 per cent, have exacerbations requiring changes in drugs, or they have failed to benefit from any drug or mixture tried. In some patients the development of severe mental disturbance [14] reduces the beneficial effect of some of these drugs to such a degree that tolerance seems to have developed, making a change of medication necessary. In the same manner, the development of pain, either unilateral or bilateral, usually fails to respond to the beneficial effects of drugs and alters the picture of a success to a failure. In two subjects surgical treatment for the pain primarily changed failure of the drug therapy to success when its use was tried after the operation.

SUMMARY

The many different forms of treatment for Parkinson's disease used in the last 135 years are mentioned. The fact that no treatment for this condition produces a result comparable to that of insulin in diabetes is discussed and stressed.

The difficulties of assessing therapy are emphasized, and an outline of various testing procedures that are necessary is described. The various forms of treatment in use at the present time are discussed. The details of the therapeutic index for the various drugs used are described, and the results of these drugs are shown in tabular form.

14. Schwab, R. S.; Prichard, J. S., and Fabing, H.: Psychiatric Symptoms in Parkinson's Disease, Am. J. Psychiat., to be published.

A NEW PROCEDURE FOR ACTIVATED ELECTROENCEPHALOGRAPHY

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NEW YORK

A CERTAIN number of clinically abnormal patients have normal electroencephalograms. Various technics have been devised to demonstrate hidden, latent or subclinical electrical abnormalities. Of these procedures, overbreathing is used routinely by most electroencephalographers. Vasopressin injection U. S. P. (pitressin®) and hydration [1] are known to demonstrate abnormalities otherwise not obtainable. On the other hand, Kaufman, Marshall and Walker [2] found that slow injection of 1 to 4 mg. of pentylenetetrazole U. S. P. (metrazol®) intravenously brought out clinical seizure patterns in epileptic patients with less discomfort to the subject than did vasopressin. A useful method, according to Gibbs,[3] is the electroencephalographic recording during natural or induced sleep. Other measures, such as the use of lobeline and insulin by Bugnard and co-workers [4] or the inhalation of mixtures of carbon dioxide and oxygen (Baudouin and associates [5]) have been employed.

In this preliminary report observations will be described which may reveal that the number of normal electroencephalograms in clinically abnormal patients is smaller than has been supposed.

METHODS AND FINDINGS

The data to follow were collected from electroencephalographic recordings taken simultaneously with or after injection of air into the subarachnoid spaces, in the usual manner for pneumoencephalography.

From the Neurosurgical Services of Lincoln Hospital and Lenox Hill Hospital.

Presented at the Fourth International Congress of Neurology, Paris, Sept. 5, 1949.

1. Blier, J. S., and Redlich, F. C.: Electroencephalogram in the Pitressin Hydration Test for Epilepsy, Arch. Neurol. & Psychiat. **57**:211 (Feb.) 1947.

2. Kaufman, C.; Marshall, C., and Walker, A. E.: Activated Electroencephalography, Arch. Neurol. & Psychiat. **58**:533 (Nov.) 1947.

3. Gibbs, F. A., and Gibbs, E. L.: Sleep Records in Epilepsy, A. Research Nerv. & Ment. Dis., Proc. (1946) **26**:366, 1947.

4. Bugnard, L.; Planques, J.; Grezes-Rueff, F. A., and Grezes-Rueff, C. H.: Action de la lobéline sur l'électroencéphalogramme des épileptiques, Semaine d. hôp. Paris **22**:1225, 1946. Baisset, A.; Bugnard, L.; Grezes-Rueff, F. A.; Grezes-Rueff, C. H., and Planques, J.: The Effect of Intravenous Insulin on the Electroencephalogram of Epileptics, read before the International Electroencephalographic Society Meeting, London, July 1947; cited by Schwab, R.: Electroencephalography, in Spiegel, E. A.: Progress in Neurology and Psychiatry, New York, Grune & Stratton, Inc., 1948, vol. 3.

5. Baudouin, A. R.; Remond, A., and Delarue, R.: Effet thérapeutique de l'inhalation d'un mélange à 70 p. 100 d'oxygène et 30 p. 100 d'anhydride carbonique (carbonacose), Bull. Acad. nat. méd. **131**:483, 1947.

The term "pneumoelectroencephalography" will be used to identify this combined method. No medication was used for at least 48 hours prior to the recording of any electroencephalogram. The same standard conditions of filters, speed of paper, damping, etc., were maintained for the records to be compared.

The results obtained under these conditions may be summarized as follows:

1. The electrical activity of normal patients was not changed by aerography.

The group of normal patients, considered to be without demonstrable cerebral lesions, were those with intractable headaches of alleged post-traumatic origin whose repeated electroencephalograms were normal. Air encephalography was decided on as a therapeutic, rather than a diagnostic, procedure. In these patients the electroencephalograms remained unchanged for several days after the complete absorption of air and during the fractional replacement of up to 100 cc. of cerebrospinal fluid with injections of air through a lumbar puncture needle. The hyperventilation records also remained unchanged.

2. Borderline normal or mildly abnormal recordings became obviously abnormal with aerography if they had an underlying abnormal electrical activity.

Fig. 1 (case 1).—Pneumoencephalogram for a 12 year old white boy with clinical seizures and repeated "borderline normal" electroencephalograms, taken after injection of 20 cc. of air. Diffuse electrical disorganization was demonstrated.

CASE 1.—E. K., a 12 year old white boy, was admitted to Lenox Hill Hospital in March 1948, because of grand mal seizures, which had increased in frequency during the previous two years.

Neurological examination revealed no abnormal signs. The blood cell counts, hemoglobin, urine, sugar tolerance and nonprotein nitrogen and urea nitrogen of the blood were normal. Roentgenograms of the skull and chest were without significance.

Repeated electroencephalographic recordings were normal. The pneumoencephalogram, taken after 20 cc. of air was injected, showed a normal condition except that the left ventricle was slightly larger than the right. The pneumoelectroencephalogram revealed marked diffuse disorganized electrical activity (fig. 1).

The final diagnosis was idiopathic epilepsy.

Comment.—A borderline normal electroencephalogram changed to one of diffuse disorganization, consistent with the clinical picture of grand mal seizures. The pneumoelectroencephalogram was the only other objective demonstration of the existence of a convulsive disorder, and the patient responded to anticonvulsant medication.

3. A dysrhythmia became grossly increased and magnified with aerography.

CASE 2.—An Arab aged 49 was admitted to Lincoln Hospital on May 11, 1948, because of a head injury sustained as the result of a fight. Unconsciousness did not follow the injury. There were intermittent periods of drowsiness, restlessness and disorientation. The presence of a subdural hematoma was suspected.

Neurological examination revealed no abnormal signs. There were laceration of the lower lip, bleeding from the mouth, nose and left ear, and hematoma of the right parietal region. The blood cell counts, hemoglobin and urine were normal.

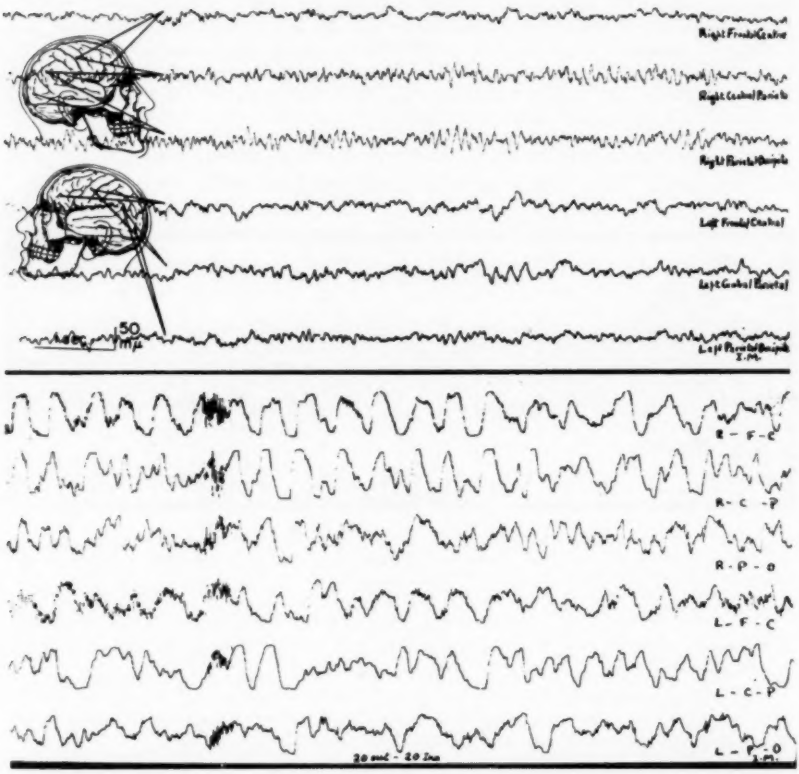

Fig. 2 (case 2).—A 49 year old Arab sustained a head injury, which was followed by prolonged drowsiness. The electroencephalogram (above) presented moderate intermittent slowing and minimal bilateral differences in amplitude. After pneumoencephalography with 20 cc. of air, bursts of 2 to 3 per second frequency and very high amplitudes were recorded (below).

A roentgenogram revealed a linear fracture of the right parietal region.

Lumbar puncture on admission yielded bloody fluid under an initial pressure of 250 mm. of water. Five days after admission the fluid was light pink and under an initial pressure of 130 mm. of water.

Repeated electroencephalographic recordings demonstrated no specific abnormalities, but only an intermittent, mild, diffuse, disorganized electrical activity, with occasional amplitudes from the left hemisphere which were slightly higher and slower than normal (fig. 2, above).

The pneumoencephalogram taken with 20 cc. of air on the thirty-fifth day of hospitalization was normal. The pneumoelectroencephalogram showed bilaterally synchronous bursts of very high and slow activity (fig. 2, below).

The procedure was followed by rapid recovery. The patient was given phenobarbital, ½ grain (0.032 Gm.), twice a day. He was discharged on June 23.

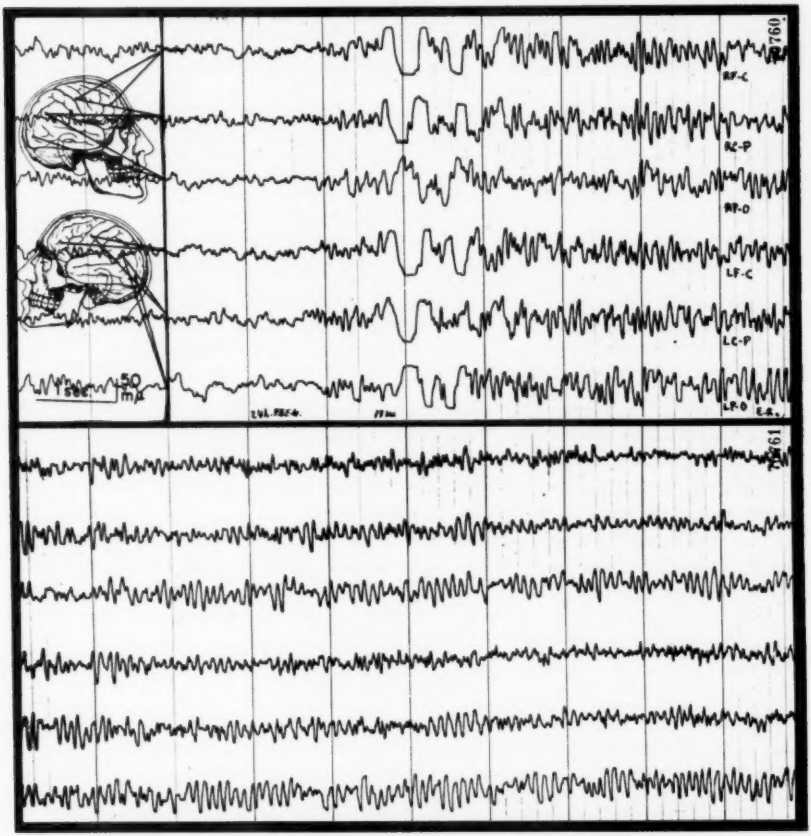

Fig. 3 (case 3).—A white man aged 55 had a history of five attacks of unconsciousness without convulsions and with an aura of "bad smell." Electroencephalograms were normal. After pneumoencephalography, with injection of 65 cc. of air, bursts of bilaterally synchronous slow frequencies of high amplitudes were obtained. The strip shown in this figure is from an electroencephalogram taken 24 hours after aerography, when the bursts were more obvious than at any other time. Forty-eight hours after pneumoencephalography the electrical activity was again normal.

The final diagnosis was (1) cerebral concussion, cortical lacerations and contusions; (2) subclinical epilepsy, either post-traumatic or idiopathic, and (3) fracture of the vault and base of the skull.

Comment.—The tendency to intermittent, slightly slower and higher amplitudes than normal changed to bursts of 2 to 3 per second of high amplitude. Therefore,

a minor abnormality became greatly magnified without losing its main characteristic, i. e., a more obvious slowness; higher amplitudes were recorded, but spikes, sharp or other wave forms, fast activity or other frequency abnormalities were not elicited.

4. Normal electroencephalograms of patients with clinical siezures became abnormal and demonstrated pathological electrical discharges with the use of pneumoelectroencephalography. This change occurred also in cases in which the hyperventilation activity was better organized than the electrical patterns preceding overbreathing.

Case 3.—E. R., a white man aged 55, was admitted to Lincoln Hospital on March 17, 1949 during an episode of unconsciousness. He had had five other such attacks during the previous year, all of sudden onset and preceded by a "bad smell." Loss of consciousness lasted five to 10 minutes, without convulsions or incontinence of urine or feces.

Examination revealed a normal status. The cell counts, hemoglobin and urine were normal. Roentgenograms of the skull and chest revealed nothing abnormal. Repeated electroencephalographic recordings were normal. The pneumoencephalogram, with injection of 65 cc. of air, was normal. Bilaterally synchronous high amplitude discharges were more obvious in the pneumoelectroencephalogram 24 hours later. A return to the prepneumoelectroencephalographic pattern occurred after 48 hours. Recovery from the air studies was uneventful. Attacks were controlled with medication. The patient was discharged April 27.

The final diagnosis was idiopathic epilepsy.

Comment.—In this case the electroencephalograms were normal. Two periods of hyperventilation presented better organized alpha rhythms from the occipital lobes than the preceding overbreathing pattern. Immediately after pneumoelectroencephalography a bilaterally synchronous burst, more pronounced from the left hemisphere than from the right, was demonstrated.

Twenty-four hours after pneumoencephalography more obvious bursts (fig. 3), dysrhythmias and poor organization were present, with an intermittent pattern of normal electrical activity.

Twenty-four hours later there was a return to the normal electroencephalographic recordings which preceded the injection of air.

COMMENT

Prior to this report, no correlation of electroencephalographic changes during and after pneumoencephalographic studies has been made, to my knowledge, and none has been reported in the medical literature.

It appears from the foregoing results that air encephalography does not change the electroencephalographic patterns in normal persons or the patterns from cortical regions not affected by abnormal electrical activity.

This method of recording the electrical activity of the brain brings out hidden dysrhythmias not demonstrable by routine electroencephalography and may localize lesions in patients whose previous electroencephalographic pattern was normal or of questionable abnormality.

The method may prove useful in the occasional case of brain tumor in which air studies (pneumoencephalography and/or ventriculography) reveal no abnormality and in which the electroencephalogram shows no localizing abnormalities.

It also adds information in cases of clinical convulsive disorders in which air studies are inconclusive or reveal no abnormality. The seizure patterns recorded by pneumoelectroencephalography have not yet resulted in any clinical manifestation.

The studies reported were carried out with injection of 20 to 100 cc. of air. Apparently, no specific quantity of air is needed. Only the amount necessary for adequate roentgenologic visualization of the ventricular and subarachnoid spaces should be used.

Appearance of the abnormality takes place during, immediately after or 24 hours after the air encephalogram.

This procedure is recommended in all cases of epilepsy, brain tumor and post-traumatic or other intracranial condition in which pneumoencephalography is indicated.

The study of a greater number of cases will be necessary before the method is considered of value as a diagnostic aid.

SUMMARY

Electroencephalographic findings during and after pneumoencephalography are presented and discussed.

Simultaneous electroencephalographic recording during and after pneumoencephalography is advised as a means of bringing out latent abnormalities which cannot be demonstrated by routine examinations.

The term pneumoelectroencephalography is proposed for this procedure.

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AN IMPROVED TECHNIC FOR PERCUTANEOUS CEREBRAL ANGIOGRAPHY

A Preliminary Report

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STACY L. ROLLINS Jr., M.D.
AND
RICHARD M. PADDISON, M.D.
PHILADELPHIA

CEREBRAL angiography can be performed by open surgical procedure, with direct injection of the common carotid artery, or by percutaneous needle puncture of the carotid artery. The open technic is time consuming, is a surgical procedure and leaves an unsightly scar. The percutaneous method also has disadvantages, such as the possibility of the injection of opaque medium into the perivascular tissues and the danger of manipulating the head while the needle is in the artery.

One of us (D. C. D.) thought these disadvantages of the percutaneous technic could be overcome and devised the following modification: With the patient on a fluoroscopic table, and after the usual preparation for a minor surgical procedure, the common carotid artery is palpated, and the point of maximum pulsation is found. With the use of local anesthesia, percutaneous puncture of the artery is performed. We have been using a 3 inch, 17 gage Huber point needle of special design (fig. 1). The hub plate permits greater control of the needle, and the Huber point is less traumatic than an open bevel point. The stylet is used to facilitate skin puncture but is removed before arterial puncture. After a successful arterial puncture, a small radiopaque catheter is threaded through the needle and up the internal carotid artery. (This method did not originate with us, since Radner [1] had previously reported vertebral artery angiography, using the catheter method.) Under fluoroscopic control, the catheter is passed until its tip is well into the artery. The needle is then withdrawn. Continuous, slow injection of sterile isotonic sodium chloride solution through the catheter is employed to prevent blockage.

From the Departments of Neurology, Radiology and Neurosurgery of the Jefferson Medical College Hospital.

† The death of Dr. Donald, the originator of the technic, in July 1949 considerably delayed the pursuit of this project. The co-authors are now continuing this work, and further refinements are anticipated.

1. Radner, S.: Intracranial Angiography via the Vertebral Artery: Preliminary Report of a New Technique, Acta radiol. **28**:838-842, 1947.

Using a syringe system, a colloidal suspension of thorium dioxide (thorotrast®) is injected as rapidly as possible, and the roentgenologic exposure is made while the last cubic centimeter is being injected. With the catheter tip just proximal to the carotid sinus, 5 cc. of the thorium dioxide suspension has produced satisfactory results. The catheter is left in place, and irrigation with saline solution is continued during the processing of the films. This permits the taking of repeat angiograms if they are required. After a satisfactory study has been obtained, the

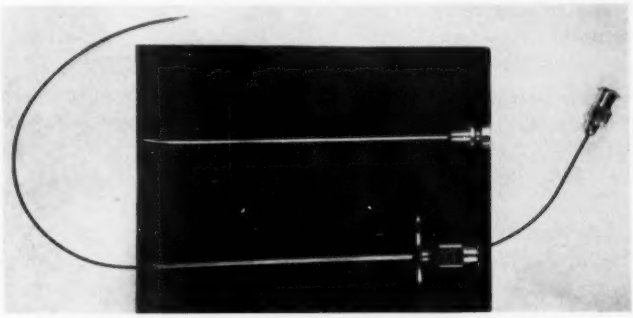

Fig. 1.—Above, stylet for needle. Below, Huber point needle with catheter in situ. The hub on the catheter is an adapter for a Luer-Lok® syringe.

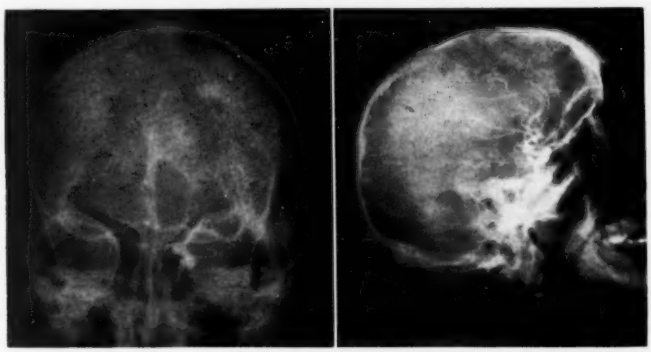

Fig. 2.—Posteroanterior and lateral roentgenograms of the skull, showing percutaneous catheter injection of 5 cc. of colloidal thorium dioxide suspension (thorotrast®) into the left internal carotid artery, with bilateral filling. Note the position of the catheter in the internal carotid artery.

catheter is withdrawn. Gentle digital pressure over the site of puncture maintains adequate hemostasis.

COMMENT

The percutaneous catheter method has definite advantages over routine percutaneous needle method of arteriography. Obviously, the opaque medium cannot be injected into the perivascular tissues, nor will the external carotid artery be filled inadvertently. Moreover, there is less trauma to the intima of the artery, since the

needle is withdrawn before the patient's head is moved. As there is no danger of displacement of the catheter, the patient may be moved to a different radiographic machine, and the head may be manipulated safely in all planes. The high position of the catheter tip decreases the dilution of the opaque medium, and therefore less medium is required. Recently, larger needles (15 and 16 gage) and catheters have been used safely, permitting rapider injection of the thorium dioxide or the use of idopyracet injection U. S. P. (diodrast®).

This method has been used in seven cases. There have been no untoward reactions, and satisfactory results have been obtained. The accompanying (fig. 2) shows the result in one case.

SUMMARY

An improved technic for percutaneous carotid angiography is described, and the equipment is illustrated.

The advantages of the technic are discussed.

THE MECHANISM OF CHVOSTEK'S SIGN

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THE INCREASED mechanical irritability of the peripheral nerves in tetany was described by Chvostek [1] in 1876 and 1879. Only the excessive irritability of the facial nerve, however, was named after him. He recommended percussing the facial nerve in front of the external auditory meatus and claimed that the muscular contraction evoked was not a reflex, but was due to "direct stimulation of the facial nerve."

Schultze [2] observed that Chvostek's sign could also be easily evoked by percussion of an area between the corner of the mouth and the zygomatic arch. The responses to this mode of stimulation are now often called Chvostek signs II and III, according to the extensiveness of the response within the muscles supplied by the middle facial branch. The Chvostek sign is often present in this form only. In some cases of tetany Schultze observed, moreover, that with percussion of the middle branch muscles within the upper facial branch contract even though the branch is not directly tapped. He realized that the response looked very much like a reflex but concluded that it was due to the spread of mechanical stimulation to the upper branch.

Van der Elst [3] agreed that the Chvostek sign, customarily evoked among neurologists by percussion of the nerve in front of the external auditory meatus, was not a reflex. He claimed that Chvostek signs II and III, used chiefly in pediatrics, were reflexes elicited from receptors mainly in the deep structures of the point stimulated. The chief arguments for the reflex theory were (1) that muscles belonging to the upper facial branch may contract even though the branch is not directly tapped and (2) that it is possible to evoke the phenomenon by thermal stimulation of the skin and mechanical stimulation of the gums, avoiding stimulation of the middle branch of the facial nerve. Finally, the phenomenon disappeared when the maxillary nerve was blocked with procaine, as tested, on one occasion, by the author on himself. Pavel, Claudian and Cornateano,[4] furthermore, found

From the Department of Clinical Neurophysiology, Serafimerlasarettet, Stockholm, Sweden.

1. Chvostek, F.: Beitrag zur Tetanie, Wien. med. Presse **17**:1201, 1876; **20**:1201, 1879.

2. Schultze, F.: Über Tetanie und die mechanische Erregbarkeit der Nerven, Deutsche med. Wchnschr. **8**:276, 1882.

3. van der Elst, P. R.: Over het verschijnsel van Chvostek en den Gelaatreflex, Inaug. Dissert., Amsterdam, 1928; Das Chvosteksche Phänomen, Jahrb. f. Kinderh. **123**:288, 1929.

4. Pavel, I.; Claudian, J., and Cornateano, D.: La signification clinique et physio-pathologique du signe de Chvostek, Ann. méd. **27**:86, 1930.

Chvostek sign II exaggerated on the hemiplegic side in four of nine patients examined. They agree that Chvostek signs II and III are reflexes. Weingrow [5] designated the Chvostek sign a myotatic reflex.

Another line of explanation has been put forward, among others by Parhon and Schachter,[6] who found Chvostek sign II preserved in peripheral facial paralysis. They concluded that the Chvostek sign was due to direct mechanical stimulation of the muscles.

In the past the only argument against the Chvostek sign's being a reflex has been that it is apparently due to direct mechanical stimulation of the facial nerve. The nature of the phenomenon was therewith considered proved. However, the facial nerve is by most authors considered a mixed nerve (Davis [7]; Carmichael and Woollard [8]; Bruesch [9]; Pearson,[10] and others). Moreover, the branches of the facial nerve anastomose freely with the trigeminal branches. Mechanical irritation may thus also stimulate afferent fibers and give rise to a reflex, such as is generally found on electrical stimulation of other mixed nerves of the body (Hoffmann [11]; Magladery and McDougal,[12] and others). Because of this, and the contradictory opinions advanced, the nature of the Chvostek sign has been studied by proper timing of the events.

MATERIAL AND METHODS

The material consisted of five adult subjects (cases 1 to 5) with latent tetany in whom the Chvostek sign was evoked by percussion at a point in front of the external auditory meatus. Ten other normal adults (cases 6 to 15) were examined in whom a Chvostek sign appeared only when a point midway between the corner of the mouth and the zygoma was tapped.

The action potentials of the contracting muscle were recorded bipolarly with pad electrodes connected to a condenser-coupled amplifier operating one beam of a cathode ray tube. The other beam was connected to an oscillator for time recording.

The Chvostek sign was elicited by a quick tap with a flat light metal shaft. The contact with the skin started the sweep of the cathode ray, and the course was recorded on film. Instead of mechanical stimulation, electrical stimulation with rectangular shocks of 0.2 millisecond's duration was used as a control in some experiments. The facial nerve was then stimulated bipolarly with pad electrodes placed close together over the nerve.

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5. Weingrow, S. M.: Facial Reflexes, Arch. Pediat. **50**:234, 1933.

6. Parhon, C. L., and Schachter, M.: Paralysie faciale périphérique et signe de Chvostek, Bull. et mém. Soc. d'endocrinol., 1937, p. 31. Schachter, M.: Paralysie faciale périphérique et signe de Chvostek (à propos de trois cas personnels), Praxis **35**:542, 1946.

7. Davis, L. E.: The Deep Sensibility of the Face, Arch. Neurol. & Psychiat. **9**:283 (March) 1923.

8. Carmichael, E. A., and Woollard, H. H.: Some Observations on the Fifth and Seventh Cranial Nerves, Brain **56**:109, 1933.

9. Bruesch, S. R.: The Distribution of Myelinated Afferent Fibers in the Branches of the Cat's Facial Nerve, J. Comp. Neurol. **81**:169, 1944.

10. Pearson, A. A.: The Roots of the Facial Nerve in Human Embryos and Fetuses, J. Comp. Neurol. **87**:139, 1947.

11. Hoffmann, P.: Untersuchungen über die Eigenreflexe (Sehnenreflexe) menschlicher Muskeln, Berlin, Springer-Verlag, 1922.

12. Magladery, J. W., and McDougal, D. B., Jr.: Electrophysiological Studies of Nerve and Reflex Activity in Normal Man: I. Identification of Certain Reflexes in the Electromyogram and the Conduction Velocity of Peripheral Nerve Fibres, Bull. Johns Hopkins Hosp. **86**:265, 1950.

RESULTS

Tapping on a point in front of the auditory meatus (case 1) elicited a response within the middle facial branch. A brisk twitch was observed in the upper lip, philtrum and ala nasi. The accompanying action potentials recorded from the philtrum appeared as a well synchronized volley after a latency of 3.75 milliseconds (fig. 1 *A*), but no further response appeared. Submaximal or maximal electrical stimulation at the point tapped evoked a similar volley after a somewhat shorter latency, 3.5 milliseconds (fig. 1 *B*). The latency of the mechanically evoked volley was 0.25 millisecond longer than that electrically evoked. The difference in latency varied somewhat according to the briskness of the blow but was short enough to

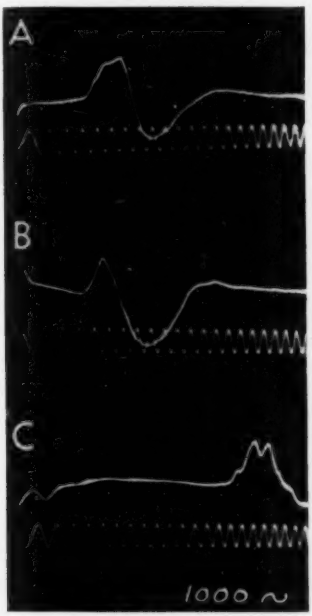

Fig. 1 (case 1).—Action potential volley recorded from philtrum after (*A*) tapping on facial nerve in front of auditory meatus (latency, 3.75 milliseconds); (*B*) maximal electrical stimulation at same spot (latency, 3.5 milliseconds); (*C*) sudden stretching of upper lip (latency, 14.5 milliseconds).

show that the nature of the muscular contraction in the two instances is the same, that is, the result of excitation of the motor fibers in the facial nerve, and not a reflex due to stimulation of afferent nerve fibers. Of course, this is also clear from the shortness of the latent period itself. The most rapid reflex response it is possible to evoke in these muscles is assumed to be caused by stretching,[13] and in case 1 came after a latency of 14.5 milliseconds (fig. 1 *C*).

In case 2 most muscles within the distribution of the three facial branches contracted with a very weak tap on a point in front of the external auditory meatus.

13. Kugelberg, E., to be published.

Here, also, the latencies were short and about the same for both maximal electrical and mechanical stimulation, showing that no reflexes were involved (fig. 2 *A*, *B*, *D* and *E*). A tap on a point midway between the corner of the mouth and the zygomatic bone also gave rise to a vigorous response at the philtrum after a latency of 2.5 milliseconds, electrical stimulation at the same spot eliciting a response with the same latency (fig. 2 *G* and *C*). On mechanical stimulation, moreover, a contraction was evoked not only within the distribution of the middle facial branch, but also within that of the upper branch, which was not directly tapped. For instance, in the procerus and frontalis muscles a contraction occurred after a latency

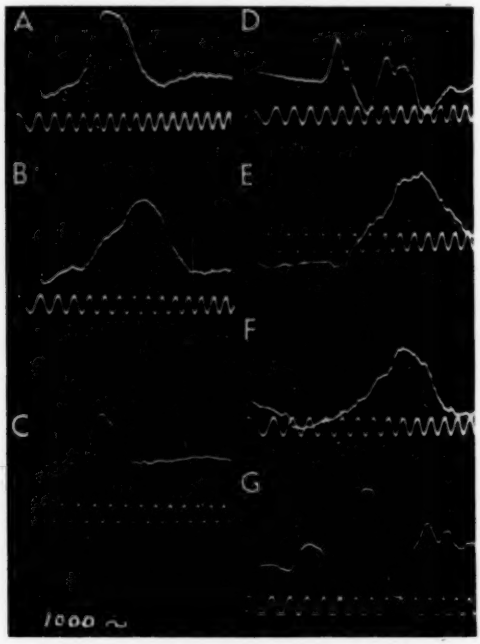

Fig. 2. (case 2).—*A* and *B*, electrical, and *D* and *E*, mechanical, stimulation at auditory meatus: *A* and *D* recorded from philtrum; *B* and *E*, from musculus procerus. *C*, electrical, and *F* and *G*, mechanical, stimulation at a point midway between auditory meatus and corner of mouth: *C* and *G* recorded from philtrum; *F*, from musculus procerus. A full description appears in the text.

of 4 to 5 milliseconds (fig. 2 *F*). The short latency excludes the possibility of a reflex. The contractions might be explained by the spread of the mechanical stimulus to motor fibers of the upper facial branch, as Schultze suggested long ago. An alternative explanation is that the motor fibers in the upper branch, hyperexcitable because of tetany, are excited through interaction. The antidromic synchronized volley in the middle branch which inevitably appears on stimulation might eventually be strong enough to excite adjacent fibers in the facial trunk distributed to the upper branches; it has been reported, for example, that the action potentials

of the heart can sometimes excite the phrenic nerve in tetany. An antidromic volley elicited by electrical stimulation of the middle branch, however, does not give rise to contractions in the forehead. Spread of mechanical stimuli was, therefore, the cause in this case.

In the group of subjects in whom Chvostek sign was evoked only by tapping over a small area midway between the corner of the mouth and the zygoma, a variable response occurred. In five of 10 subjects there was only one response after a latency of about 3.5 milliseconds, even with a relatively hard tap. Figure 3 *B* shows this response after 3.6 milliseconds, as compared with 3 milliseconds on electrical stimulation (fig. 3 *A*). Even with a slower sweep, no more discharges

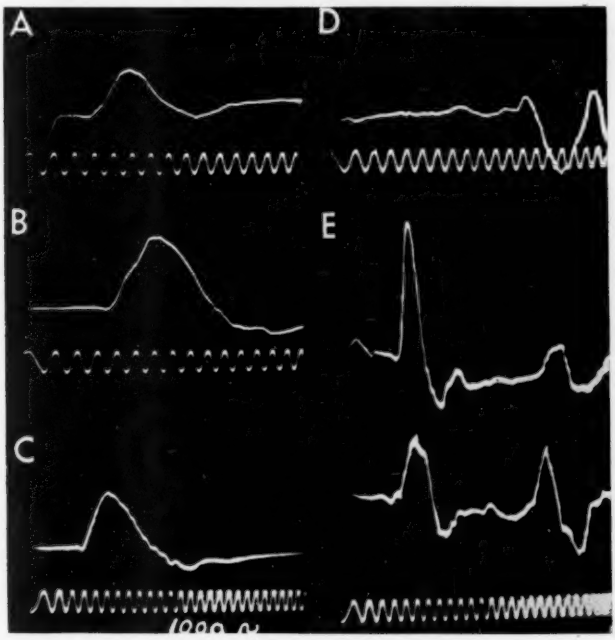

Fig. 3.—Electrical and mechanical stimulation at a point midway between auditory meatus and corner of mouth. *A-C* (case 7): Recorded at philtrum: *A*, response to electrical stimulation; *B*, response to mechanical stimulation; *C*, same as *B*, with slower speed, showing that no other response follows the direct volley. *D*, (case 7): Recorded at upper lid—a reflex response only. *E* (case 8): Recorded at philtrum: The direct response is followed by a reflex discharge.

appeared on tapping (fig. 3 *C*). In the remaining subjects usually only this early response occurred when stimuli at threshold strength were used, but with a stimulus somewhat above threshold another discharge appeared after a latency of 14 to 17 milliseconds. Sometimes the thresholds for the two responses were much the same. This is seen in figure 3 *E* (case 10), which shows, with two consecutive blows of nearly threshold strength, responses with no systematic difference in amplitude. In subjects with exaggerated facial reflexes only reflex responses may appear at the philtrum, as observed in some cases of amyotrophic lateral sclerosis.

For the orbicularis oculi the reflex thresholds are very low. A reflex contraction may be evoked by tapping over a wide area, as illustrated in figure 3 *D*. Here a tap below the zygomatic bone readily gives rise to a reflex discharge in this muscle, as does a tap on a point in front of the external auditory meatus. Thus, blinking is not a suitable index of the mechanical irritability of the facial nerve without electromyographic control because of the interference of reflexes.

COMMENT

It is clear that, although not based on valid arguments, the classic explanation of the mechanism of Chvostek's sign as elicited by tapping on the facial nerve in front of the auditory meatus is correct. The sign is not a reflex, but is due to the mechanical stimulation of motor fibers in the nerve.

Neither the classic explanation nor the reflex theory, however, is adequate for the Chvostek sign as elicited by tapping on a point midway between the corner of the mouth and the zygomatic arch. The response may often be due only to mechanical stimulation of motor fibers, occasionally only to a reflex; but in many instances, if the tap is not too weak, the muscular contractions observed are double responses, due to both.

The two modes of eliciting the Chvostek sign are not altogether comparable without electromyographic control. With the first method only the mechanical irritability of motor fibers in the facial nerve is tested. With the second method the presence also of a reflex may be tested. This may explain certain discrepancies in the opinions of various authors with regard to the clinical significance and applicability of the Chvostek sign, since the two modes of stimulation are seldom clearly distinguished.

Attempts to elicit the reflex by thermal stimulation of the skin or mechanical stimulation of the gums, as reported by van der Elst,[8] have given negative results. The short latency of the reflex, 14 to 15 milliseconds, and the well synchronized discharge are characteristic of the facial reflexes assumed to be of myotatic origin.[13]

The threshold for mechanical stimulation of the facial nerve evidently reaches one of its lowest values in the region below the zygomatic bone, probably owing to the loose consistency of the surrounding tissue. Though the threshold for eliciting reflex contractions in the muscles within the distribution of the middle branch of the facial nerve by tapping is not very low, the region is so near that mechanical stimuli are easily transmitted to the muscles, evoking reflex discharges which complicate the clinical interpretation of Chvostek signs II and III. The thresholds for reflex responses in the orbicularis oculi muscle are extremely low. Consequently, contractions in this muscle when any region of the face is tapped cannot, without exact timing of the event, be taken to be the result of a direct response due to mechanical stimulation of motor fibers in the facial nerve.

The third explanation advanced, that the Chvostek sign was due to direct stimulation of the muscles, is not supported by this work. The latency time is that of nerve stimulation several centimeters from the muscle. If the facial nerve is degenerated, the denervated hypersensitive muscles may, however, contract on mechanical stimulation at a distance of 5 to 10 cm. from the muscle, but this does not justify any general conclusions with regard to the mechanism of the Chvostek sign.

SUMMARY AND CONCLUSIONS

The mechanism of Chvostek's sign was studied by measuring electromyographically the latency time between a blow and the muscular contraction evoked. The following conclusions are drawn:

1. Chvostek's sign elicited by tapping the facial nerve in front of the external auditory meatus is due to mechanical stimulation of motor fibers, the latency being about the same, 3.5 to 4.5 milliseconds, for both mechanical and maximal electrical stimulation.

2. Chvostek's sign, elicited by a moderately hard tap between the corner of the mouth and the zygomatic bone in subjects who give this response only with this mode of stimulation, may consist of (*a*) one response only, after a latency of about 3.5 milliseconds, due to mechanical stimulation of motor fibers in the middle facial branch, or (*b*) a double response, the volley directly evoked being followed by a reflex discharge with a latency of 14 to 15 milliseconds, or (*c*) a reflex discharge only, observed in subjects with increased facial reflex excitability.

This work was facilitated by a grant from the Swedish Medical Research Council.

Abstracts of Current Literature

Diseases of the Brain

THE DIAGNOSIS OF PARAPHYSICAL CYST. J. W. D. BULL and D. SUTTON, Brain **72**:487 (Dec.) 1949.

Bull and Sutton report on a study of 24 cases of paraphysical cysts. Particular emphasis is placed on the roentgenological aspects, since the authors believe that accurate diagnosis of these lesions depends primarily on ventriculography. Plain roentgenograms showed evidence of increased intracranial pressure only in 10 of the cases. Of the 20 cases in which ventriculographic studies were carried out, the correct diagnosis was made in 19. The cyst is best seen in three views: (1) the lateral view; (2) the half-axial view with the brow up, in which the tumor is seen as an ovid defect at the lower part of the septum pellucidum, and (3) the anteroposterior view with the brow up, in which the cyst appears as a semicircular defect at the lower end of the septum pellucidum.

FRANKEL, Philadelphia.

TOXOPLASMIC ENCEPHALOMYELITIS. A. WOLF, D. COWEN and R. PLUVINAGE, Rev. neurol. **81**:262 (April) 1949.

Toxoplasmic encephalomyelitis, usually a fatal disease, is found principally in newborn and nurslings and is characterized by a tetrad of signs: (1) neurological signs, such as convulsions, appearing any time after birth, muscle twitching, restlessness, meningeal signs, xanthochromia and pleocytosis; (2) hydrocephalus, most frequently noncommunicating, and caused by lesions of the aqueduct; (3) chorioretinitis (almost always), due to retinal toxoplasmic infection, and blindness; (4) intracerebral calcifications, usually spotty or linear.

There are widespread small granulomas and zones of necrosis in various stages of disorganization and repair. They exhibit a tendency to deposition of calcium, which can be seen roentgenographically. The lesions tend to be situated periventricularly, and they may coalesce, causing subependymal necrosis and ependymal ulceration.

The disease is transmitted by an unknown medium to the pregnant mother, and thence to the fetus in utero, and is truly congenital. Infants may recover, with residual defect. The disease may be transmitted to animals from human material; this, and the presence of immune reactions, permit a diagnosis during life.

LEGAULT, Washington, D. C.

VERY SEVERE CASE OF ERB-GOLDFLAM MYASTHENIA IN A YOUNG GIRL. BILATERAL CAROTID SINUS DENERVATION (FIFTH CASE REPORTED). CLINICAL CURE IN SIX MONTHS WITH SIMULTANEOUS DEVELOPMENT OF A MEDIASTINAL TUMOR. A. THÉVENARD, Rev. neurol. **81**:469 (June) 1949.

Thévenard reports the case of a girl aged 18 who had complained of dysphagia, nasal speech and diplopia for a year and who on examination presented the classic features of myasthenia gravis with bulbar signs. This included the Jolly reaction on electrical testing and dramatic response to a diagnostic test with neostigmine. No other abnormality was noted except the presence of mild thyroid enlargement of the colloid type (basal metabolic rate + 11 per cent) and an undiagnosed irregularity of the mediastinal silhouette as seen in roentgenograms. The patient was followed for a month without medication for purposes of diagnostic study. During this time, she became bedridden; there developed total inability to swallow with severe nasal regurgitation, and just before operation she began to be dyspneic.

Bilateral denervation of the carotid sinus was done in two stages. After the first operation, on the right side, the patient almost died during an attack of sudden pulmonary edema. The

author states that preoperative medication with neostigmine is necessary. Six months after the second operation the patient had entirely discontinued the use of neostigmine and had no residual signs except for a slightly nasal speech. Routine roentgenographic examination revealed that in the meantime a mediastinal tumor had developed, probably a thymoma.

The author notes that, in spite of the growth of the tumor, the signs and symptoms of myasthenia have not reappeared. He states that myasthenia gravis is probably an endocrine difficulty in which the prime mover is the hypothalamic-pituitary complex, the thymus being a secondary reactor, and that denervation of the carotid sinus is effective because of some effect on this primary central mechanism.

LEGAULT, Washington, D. C.

SELLAR MENINGIOMA INVADING THE OPTIC CANALS. N. BLATT, M. ATHANASIU and E. WINBERG, Rev. d'oto-neuro-opht. **21**:321 (Aug.-Sept.) 1949.

The authors report the case of a patient showing symptoms of a pituitary adenoma, as well as those of a suprasellar meningioma. This distinction appeared to be an important one, for, whereas a suprasellar meningioma would require surgical intervention, an adenoma could be treated with high voltage roentgen radiation. There were no neurological signs pointing to dysfunction of the pituitary gland. Instead, the patient presented mental changes, such as severe alterations of judgment, euphoria and anosmia—symptoms pointing to a suprasellar meningioma. The sella turcica was greatly enlarged.

The authors report a method by which the important differentiation of these two tumors can be made on the basis of a precise analysis of the optic foramen in the roentgenologic picture. The sellar changes in an adenoma are due to intrasellar pressure, producing a ballooning effect. The changes produced by a suprasellar meningioma are due to invasion of the bony structures. These bony infiltrations are present also at a distance from the sella. In the present case, the stereoscopic roentgenograms of the optic foramen reveal osteoporosis of the small wings of the sphenoid bone. The optic canals were large, and in the superior region they showed erosion and interruption of their contours. These changes were indicative of a meningioma. The authors do not state whether their preoperative diagnosis was confirmed at operation.

SJAARDEMA, Los Angeles.

CEREBRAL CYSTS FOLLOWING CEREBRAL CONTUSIONS. B. BORSCHEL, Deutsche Ztschr. f. Nervenh. **160**:221 (April 9) 1949.

Borschel presents the histories of six patients in whom brain cysts developed after contusion and one in the temporal lobe. These locations corroborate the concept that the poles of the brain are predisposed to traumatic lesions. In four cases epileptic reactions resulted and led to diagnostic clarification. One patient presented a neurasthenic picture, and one had a syndrome indicating involvement of the frontal lobe. The neurological manifestations corresponded to the localization of the cyst. Contrary to observations made by Kroll, signs of increased pressure on the brain were absent. Diagnosis of the cysts requires roentgenographic study with air as the contrast medium. When there is no communication with the cerebrospinal fluid spaces, direct puncture can be performed. The differential diagnosis must rule out cystic tumors, cysts caused by parasites and cavity formations resulting from malacia or hemorrhage. In the pathogenesis one must consider the direct mechanical factors of the contused area and the circulatory factors. These may help to explain the large size of some cysts after apparently mild trauma.

J. A. M. A.

GESTATION AND MULTIPLE SCLEROSIS. J. HIRSCHMANN, Arch. f. Psychiat. **181**:530 (March 25) 1949.

Hirschmann discusses the conditions under which multiple sclerosis, when it concurs with pregnancy, may take an unfavorable course. His observations were made on 90 women with multiple sclerosis who were observed at the Clinic for Nervous Diseases in Tübingen and who

had been pregnant once or several times. The condition in cases in which pregnancy and delivery concurred with a chronic progressive phase of multiple sclerosis usually became aggravated and took an unfavorable course. The age of the patient also seemed of considerable importance in the prognosis. Women who had advanced beyond the third decade of life were in greater danger than were younger women. Since aggravation of multiple sclerosis frequently becomes manifest at a period when interruption of the pregnancy is no longer possible and since, moreover, induced abortions themselves may cause considerable exacerbation of the sclerotic process, prevention of pregnancy rather than its interruption is advisable in patients in whom multiple sclerosis takes a certain course. J. A. M. A.

PREFRONTAL LEUKOTOMY. E. MONIZ, Arch. f. Psychiat. **181**:591 (March 25) 1949.

Moniz mentions the theoretical foundations for his first attempts at a surgical treatment of certain psychoses, briefly describes the technic and reviews the development and the present status of prefrontal leukotomy. He gives particular attention to the valuable advances in psychosurgery contributed by investigators in the United States. J. A. M. A.

Diseases of the Spinal Cord

POLIOMYELITIS ATTACK RATES IN AMERICAN TROOPS, 1940-1948. J. R. PAUL, Am. J. Hyg. **50**:57, (July) 1949.

Paul shows that the rates at which United States troops contracted poliomyelitis during the years 1943 to 1948 were different in different parts of the world. They were higher in the Far East and Philippine Islands than elsewhere. As an explanation of this fact, the author suggests that it is likely that there is a large amount of poliomyelitis virus (perhaps representing a variety of strains) in areas where previously poliomyelitis had been considered as rare. Furthermore, it is likely that clinical poliomyelitis may be much more prevalent in some areas, including tropical or semitropical areas, than had previously been supposed. This impression has recently been substantiated by dispensary and hospital surveys in Palestine and Egypt and by a review of mortality statistics in Japan. In these areas, because the acute disease has been largely limited to sporadic cases in young infants, large epidemics have seldom been reported and nonparalytic cases in natives have practically never been reported, there is an erroneous impression that both the virus and the disease are rare. In such areas the clinical disease has come quickly to the surface when immigrant troops arrive. Much more research is necessary before an adequate explanation of these phenomena can be expected. J. A. M. A.

ELECTROCARDIOGRAPHIC OBSERVATIONS IN POLIOMYELITIS: CHANGES OF THE Q-T INTERVAL IN TWENTY-THREE CASES. H. A. JOOS and P. N. G. YU, Am. J. Dis. Child. **80**:22 (July) 1950.

Gefter and associates have previously reviewed electrocardiograms made from 226 patients with poliomyelitis. Abnormalities were found in the records of 32 (14.2 per cent). There was little change in the frequency of electrocardiographic abnormalities as the duration of the disease increased, suggesting that such changes occur early and tend to persist for several weeks. Clinical evidence was generally insufficient to support a diagnosis of carditis.

Measurement of the Q-T interval, corrected for rate, has recently been proposed as a diagnostic aid in the detection of active rheumatic carditis. Prolongation of the corrected Q-T interval (Q-Tc) in active carditis is said to indicate disturbed myocardial efficiency, since the systole (Q-T) of the diseased myocardium is prolonged at the expense of the diastolic resting phase (T-Q) of the cardiac cycle.

Electrocardiographic studies of myocarditis in other infectious diseases or in acute poliomyelitis have not included a discussion of the possible diagnostic significance of the Q-Tc interval. It was the purpose of this report to evaluate the cardiac status of patients during and following acute poliomyelitis, and especially to point out the changes in the Q-T interval

in the electrocardiogram as a possible diagnostic aid. Clinical and electrocardiographic observations were recorded on 23 children with poliomyelitis, and parallel observations were made on 55 control patients.

Of the 23 children with acute poliomyelitis, the Q-Tc interval was prolonged in 5 and equivocal in 3. In the control series of 55 patients, the Q-Tc interval was equivocal in 3. Joos and Yu discuss the possible diagnostic significance of the Q-Tc interval and point out the need for further clinical and pathological study. No other electrocardiographic abnormality noted was of specific diagnostic significance.

ALPERS, Philadelphia.

CARDIOPATHY IN FRIEDREICH'S ATAXIA (SPINAL FORM OF HEREDITARY SCLEROSIS). T. H. LORENZ, C. M. KURTZ and H. H. SHAPIRO, Arch. Int. Med. **86**:412 (Sept.) 1950.

Friedreich's ataxia is usually considered a relatively rare "neurological" disease, and until recently the cardiac aspects have received little attention in the American literature. The authors, in reviewing the American and European literature and the cases reported in this article, point out that cardiac involvement is a serious, and relatively frequent, concomitant of Friedreich's disease.

Analysis of the cases of five siblings having Friedreich's ataxia showed cardiac changes of remarkable similarity on auscultatory, orthodiascopic and electrocardiographic examination. The most striking and consistent changes were noted in the electrocardiogram. The tracings of the five siblings reported on showed remarkably similar changes in the T waves when compared both with each other's and with those in the literature. This pronounced similarity renders simple coincidence highly improbable.

Lorenz and his co-workers believe that greater emphasis and more active investigation should be directed toward this disorder from the standpoint of both organ systems involved, and that the disease should be regarded as systemic rather than purely neurological.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

MULTIPLE SYMMETRIC BILATERAL CRANIAL NERVE PALSIES IN PATIENTS WITH UNREGULATED DIABETES MELLITUS: REPORT OF THREE CASES. D. L. LARSON and J. H. AUCHINCLOSS, Arch. Int. Med. **85**:265 (Feb.) 1950.

The mechanism of the production of peripheral neuropathy in diabetes has not been definitely established, but it appears to bear some relation to inadequate regulation of the disease. The lower extremities are commonly more severely affected than the upper, and the neurological findings in general are those of a mixed polyneuropathy involving the motor and sensory nerves. Paralysis of cranial nerves is usually unilateral or asymmetrical; bilateral symmetrical involvement has been mentioned only infrequently in the literature.

In the present communication extensive bilateral, symmetrical paralyses of cranial nerves are reported in three patients with inadequately controlled diabetes mellitus. All three patients had diabetes of four to 12 years' duration, requiring moderate amounts of insulin. In each case there was a background either of poor diabetic control or of inadequate supervision, and two of the patients exhibited strikingly labile diabetes throughout the course of hospitalization. In no case was there a history of antecedent neurological disease. In all three patients bilateral symmetrical multiple paralyses of cranial nerves developed rapidly; in two patients they made their first appearance after the correction of severe diabetic acidosis. In each case severe polyneuropathy involving the peripheral nerves began at the same time as or followed the onset of the neuropathy of the cranial nerves. At some time during the acute illness, spinal fluid protein values were moderately elevated, while the number of lymphocytes was only

slightly increased. In all cases recovery was practically complete within three months. There were residual pains in the extremities in two cases, but these subsequently disappeared over the course of several months, with satisfactory diabetic regulation.

ALPERS, Philadelphia.

STREPTOMYCIN TOXICITY OF THE EIGHTH NERVE. D. J. PEIK, HOWARD HIGH and P. A. CAMPBELL, Arch. Otolaryng. **50**:251 (Sept.) 1949.

Twenty-one men, between the ages of 21 and 58, who were receiving streptomycin treatment for moderately or far advanced pulmonary tuberculosis were carefully examined at frequent intervals to determine the effects of the drug on the eighth nerve. All patients received 2 Gm. of streptomycin dihydrochloride daily for 120 days. Observations showed that all patients experienced vestibular dysfunction, but none experienced loss of hearing. The appearance, progression and duration of vertigo followed the reduction in the caloric response almost exactly. It was noted that the older men of the group suffered severe vestibular loss, and recovery seemed slower and less complete than in the younger men. These patients were observed up to 11 months after cessation of treatment, at which time only four had normal vestibular function.

RYAN, Philadelphia.

IDIOPATHIC PARALYSIS OF THE VOCAL CORD. EMIL GLAS, Arch. Otolaryng. **50**:612 (Nov.) 1949.

Idiopathic paralysis of the vocal cord is defined as paralysis in which the nerve itself is involved, without external pressure. This involvement seems to be a neuritis affecting all the fibers of the inferior laryngeal nerve, producing a "cadaveric" cord. Paralysis of this type is not slowly progressive, but the cadaveric position is assumed at the onset.

Glas observed five patients showing idiopathic immobilization of the vocal cord, all on the right side. A sudden change in quality of the voice and abnormally quick vocal fatigue were noted. In all the patients a slight pain was produced on pressure between the trachea and the esophagus along the course of the inferior laryngeal nerve. Glas considers the latter a pathognomonic sign of idiopathic paralysis of the vocal cord. The prognosis in true idiopathic paralysis is favorable.

RYAN, Philadelphia.

MOTOR FORMS OF HERPES ZOSTER. C. A. BARDECI, Rev. Asoc. méd. argent. **63**:326 (July 15-30), 1949.

Motor types of herpes zoster are rare and are seen more frequently in older persons. Bardeci reports the cases of two women aged 68 and 78 and a man aged 38. Paralysis occurred in all three patients immediately after the eruption and the development of the sensory symptoms. The motor paralysis involved chiefly the brachial plexus. The motor lesions were acute. They progressed in one patient to areas not involved by sensory disturbances. Improvement occurred within three months in one patient, and recovery was complete in another month. The motor disorders became stationary in the oldest patient. The type of paralysis, its coincidence with sensory involvement and the nucleoradicular character of the paralysis, as confirmed by electrodiagnosis, suggest that these types are caused by an ascending virus neuritis, which reaches the spinal ganglia through the sensory neurons of the peripheral nerve. It allows the passage of the virus to the anterior horns, through the axis-cylinders of the afferent sensory route. The virus lesions of the motor cells of the anterior horns are reversible in two to four months.

J. A. M. A.

Treatment, Neurosurgery

PERIPHERAL FACIAL PARALYSIS IN FRACTURES OF THE TEMPORAL BONE. KARSTEN KETTEL, Arch. Otolaryng. **51**:25 (Jan.) 1950.

Until the recent introduction of surgery of the facial nerve, the treatment of facial paralysis in fractures of the temporal bone was purely conservative. Even though the prognosis with

this type of therapy was considered favorable, Kettel outlines the indications for surgical intervention in selected cases of fracture with damage to the facial nerve.

Fractures of the temporal bone are divided into two main types—longitudinal and transverse. The longitudinal fracture is commonest and has the better prognosis for both life and cochlear and vestibular function. Facial paralysis occurs far more frequently with transverse fractures than with the longitudinal type. The appearance of the facial paralysis may be either immediate or delayed, the prognosis for the delayed type being more favorable with conservative treatment.

Kettel concludes that in cases of immediate paralysis an exploration of the facial nerve should be done as soon as the patient's general physical condition permits, provided a final diagnosis of a severe lesion of the nerve in an accessible place has been made. If this is not possible and no signs of returning function are noted after two months of observation, a severe lesion must be suspected, and decompression is then indicated. Even in the case of delayed paralysis the same procedure should be followed if after two months no return of function is noted. If there is no muscular atrophy and the site of damage is localized, exploration may lead to eventual limited improvement, even in cases of long-standing paralysis. In any case, muscular function should be kept alive by stimulation and massage until repair and reinnervation have been accomplished.

RYAN, Philadelphia.

Encephalography, Ventriculography and Roentgenography

THE ROENTGENOLOGIC MANIFESTATIONS OF ACOUSTIC NEUROMAS. B. S. EPSTEIN, Am. J. Roentgenol. **64**:265 (Aug.) 1950.

Epstein found considerable variation in the percentage of roentgenologic changes encountered in cases of acoustic neuroma. Some authors found practically no significant bony changes in most cases, whereas others found changes on plain roentgenograms in 90 per cent of cases. The author's series consisted of 21 cases of proved acoustic neuroma. Significant changes were demonstrated in approximately 30 per cent of the cases. The author finds the Towne and preorbital views of the petrous pyramids the most advantageous. Evidences of increased intracranial pressure on plain roentgenograms were infrequent. The positive findings consisted of decalcification and widening of the internal auditory meatus.

Seven patients with no significant changes in the plain roentgenograms were subjected to air studies. In five cases the lateral ventricles were dilated. In one case in which the lateral ventricles were not seen in the encephalogram there was an elevation of the callosal sulcus, indicating the presence of hydrocephalus. In one case there were a slight narrowing and upward and lateral displacement of the temporal horn, and in another the occipital horn was elevated.

The third ventricle was dilated in three cases. In one case the third ventricle was displaced away from the side of the lesion. The sylvian aqueduct was seen in five cases; it was displaced away from the midline in three cases and was displaced dorsally in two cases.

The fourth ventricle, well visualized in five cases, was displaced posteriorly in three, as indicated by measurements from the floor of the dorsum sella to the fourth ventricle. In two cases the depth of the cisterna pontis was diminished, and in one case the cisterna ambiens was not filled. Apparently, the findings on pneumoencephalographic examinations depend on the changes in the posterior fossa arising from the tumor. If these are minimal, the encephalogram may disclose only slight or moderate hydrocephalus, with neither distortion nor displacement of the cerebrospinal fluid passages in the midline. When the tumor extends laterally and upward, there is more likely to be pressure against the aqueduct and the posterior aspect of the third ventricle, whereas with tumors which further encroach downward toward the foramen magnum variations in the configuration and position of the fourth ventricle may occur. For the most part, the author's findings on roentgenograms made after air study in cases of proved acoustic neuroma agree substantially with the numerous reports in the literature.

TEPLICK, Philadelphia.

Congenital Anomalies

CONGENITAL ABSENCE OF PECTORALIS MAJOR MUSCLE IN WHOLE OR IN PART AND ABSENCE OF PECTORALIS MINOR MUSCLE (UNILATERAL): REPORT OF 3 CASES. W. M. HAYES, South. Surgeon **15**:417 (June) 1949.

Hayes reviews the literature on congenital absence of pectoralis muscles and describes three patients whom he had observed. The first patient was a man with congenital absence of the pectoralis major and minor muscles on the right side. The second patient was a man with congenital absence of the sternocostal portion of the pectoralis major muscle. The clavicular portion of the muscle was present and well developed. The pectoralis minor muscle was also absent on the right side. The third patient was a woman with congenital absence of the pectoralis major and minor muscles on the left side. There was little breast tissue, and this did not function. The woman also had bilateral cervical rib. The sternocostal portion seems to be that portion which is most commonly missing.

J. A. M. A.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Alex J. Arieff, M.D., Past President, in the Chair

Regular Meeting, Nov. 14, 1950

Effect of Sympathectomy and Thiocyanates on the Adrenal Cortex. Dr. Joseph Tarkington, Hines, Ill.

The complementary action of sympathectomy and thiocyanates in the treatment of essential, or high diastolic, hypertension has been noted and verified clinically. The site or mode of action of the thiocyanates was unknown until recent work showed the adrenal cortex to be one site of action of these drugs. The present experimental work showed changes in the lipid distribution and content of the adrenal cortex in hypertensive animals similar to those found in clinical patients who are treated with cyanates alone and with sympathectomy plus thiocyanates. That there is a greater depletion of lipids in the adrenal gland after sympathectomy and cyanate therapy than after treatment with cyanates alone was clearly demonstrated. Such a depletion explains why the clinical benefit obtained is greater with combined treatment than with either alone.

DISCUSSION

Dr. H. R. Strong: It is not entirely clear what was done in the way of denervation of the adrenal gland and what were the effects on the adrenal gland of more extensive sympathectomies.

Dr. Joseph Tarkington: After a sympathectomy from the fifth thoracic through the third lumbar segment, the blood pressure of the animal dropped momentarily. After 48 hours it was stabilized. These are the results found throughout the country. The administration of cyanates later brings the blood pressure down to a much lower level.

Variability of Signs in Multiple Sclerosis. Dr. Irving C. Sherman.

A critical method of objective evaluation of the fluctuation of signs in multiple sclerosis was presented.

A group of 42 patients was observed in hospital for three weeks, and the clinical status at discharge was compared with that on admission. Of 466 pathological signs, there were 69 signs of improvement among 32 patients and, at the same time, 39 signs of regression among 30 patients. Twenty-three patients were observed from three to 30 months. Comparison of the results of the initial and final examinations revealed that of 265 pathological signs there were 66 instances of improvement among 21 patients, whereas there were 58 signs of regression among 19 patients.

A more detailed analysis of the signs, which varied in frequency or intensity, was permitted by a study of repeated examinations during the course of the illness in the patients observed from three to 30 months. The most variable were cerebellar signs, clonus, the Hoffmann sign, nystagmus and bladder disorders. All other signs fluctuated at one time or another, except for speech. There also appeared several instances of the acute episodic neurological disorder so familiar in multiple sclerosis.

This study reemphasized what has been accepted as one of the diagnostic criteria of multiple sclerosis, namely, its episodic and recurrent nature in some cases. Furthermore, attention was called to the fact that there may be variability in the objective signs without the appearance of any gross episodic disorders.

DISCUSSION

Dr. Oscar Sugar: Would Dr. Sherman comment on the maintenance of abdominal reflexes in well established cases of multiple sclerosis?

DR. W. R. KIRSCHBAUM: All are familiar with a certain variability in the symptoms of multiple sclerosis—the sudden onset, the eventual gradual disappearance and the changes in intensity. The tabulations of Dr. Sherman are an excellent expression of this. It is noteworthy from his findings, however, that only certain symptoms show a decided tendency to vary. In the early cases of multiple sclerosis there is an evident tendency to improve in accordance with the localization of the pathologic process. The symptoms destined to improve are the most complex—gait, ataxia, tremor and pareses—whereas articulatory speech disturbances and changes in visual acuity and the optic disks do not vary if once clearly established. The complex symptoms may, to some extent, be substituted for and relieved by cooperative systems, depending on the extent of the demyelinated patch. This is not possible in the terminal pathways of the visual (disk) and articulatory (medulla oblongata) systems, where substitution is inadequate. Before the later stages are reached, physical therapy makes good use of improvement of complex symptoms by training.

DR. IRVING SHERMAN: With reference to Dr. Sugar's question concerning the maintenance of the abdominal reflex: The main constant finding was some abnormality in this reflex. However, the response was not always absent. If it was absent at one time, it could be elicited later. The next time there would be one "spasmodic" response, and so on. I should like to thank Dr. Kirschbaum but feel that I cannot amplify his remarks. It is my recollection that I have not seen speech improved in cases of multiple sclerosis.

Electrodiagnostic and Electromyographic Study of Muscle Denervated by Section of the Anterior Roots. DR. NORMAN B. DOBIN and DR. JAMES A. FIZZELL.

The kinetics of stimulation of the tibialis anterior (anticus) muscle of cats, the motor nerve supply of which was interrupted by an anterior rhizotomy, was studied with a square wave galvanic current over a 90 day postoperative period, with the following results:

The rheobase threshold fell, reaching its lowest level 21 days after operation. The chronaxia became lengthened. The cathodal tetanus ratio fell and reached unity 21 days after operation. Discontinuities developed in the strength duration curve as early as the seventh postoperative day. The strength interval curve for repetitive stimuli, of 1 millisecond's duration, became ascending in the direction of the greater time interval between stimuli, and the thresholds for twitch and tetanus to repetitive stimulation approached equality. Spontaneous fibrillary activity recorded electromyographically appeared as early as the seventh postoperative day.

These findings, indicative of denervation, parallel the kinetics of stimulation of muscle in instances of peripheral nerve lesions, in which both motor and sensory pathways are interrupted.

DISCUSSION

DR. ALEX ARIEFF: In reviewing data on paraplegic patients undergoing rhizotomy for spasm, I selected a patient who had electrodiagnostic tests before and after operation. For two muscles which I selected the rheobase did not change much but was lowest about 60 days after rhizotomy. The tetanus ratio was low in one muscle at the twenty-fourth and, again, at the sixtieth day. The low point in the other muscle was on the thirty-first and sixtieth day. From then on the tetanus ratio was not quite normal but was usually higher than 2.0. When electromyographic recording was done up to 118 days and as early as 14 days after operation, fibrillation was found in only a few instances, but at most times the muscle was silent. Rhizotomy was done years after the original injury. What is Dr. Dobin's opinion about the increased tetanus ratio in the human subject 80 to 90 days after operation? Is there spontaneous neurotization, or were roots possibly not cut at operation? If all roots remained cut, the denervated muscle should have a low tetanus ratio and should fibrillate more than we observed.

DR. NORMAN B. DOBIN: I believe that 80 days after rhizotomy there is some spontaneous recovery.

Reflexes Evoked by Stimuli of Cold in Injuries to the Spinal Cord. DR. LEWIS J. POLLOCK and DR. JOHN FINKLE (Hines, Ill.).

As was expected, the stimulus of cold, like other exteroceptive stimuli, produced reflex activity from the distal end of an injured spinal cord.

The effectiveness of the stimulus was less than that of scratch or multiple pinprick. The responses occurred from stimulation of similar reflexogeneous zones.

As with other stimuli, the greatest number of muscle groups participating in the reflexes occurred with injury of the cervical portion of the spinal cord; next, with injuries of the thoracic, and least, with injuries of the lumbar portion. Crossed reflexes occurred least frequently with lesions of the lumbar portion of the spinal cord, next frequently with thoracic lesions and most frequently with cervical lesions. With cervical lesions of the spinal cord abnormal reflex activity in the upper extremities occurred from stimulation of the upper extremities.

Ipsilateral and contralateral reflexes of the upper extremities were evoked by stimuli below the level of the lesion—in a few cases as low as the inner thigh. Stimulation of the upper extremity resulted in reflex movements of the lower extremities in two cases.

Joseph A. Luhan, M.D., President in the Chair

Regular Meeting, Dec. 12, 1950

The Bodily State in Injuries of the Spinal Cord. Dr. Herman Chor, Dr. Isidore Finkelman, and Dr. Herman Blustein.

A study was made of various important components of the bodily state in a group of patients with injuries of the spinal cord.

The basal blood pressure was found to be low with lesions of the cervical portion of the cord, and there was no increase in blood pressure proportionate to age. Orthostatic hypotension occurred oftenest with lesions of the cervical part of the cord. Hypotension caused "blackout," and the reflex hypertension with headache occurred during the administration of enemas. There was a defect in concentration of urine, as well as in the day-night ratio, although no signs of renal disease were noted. Glucose tolerance curves were abnormal, although there was no evidence of disease of the liver, pancreas, adrenal glands or thyroid. There was stasis of the colon, as determined by charcoal excretion tests. Evacuation and concentration of the gallbladder were normal. Diarrhea was occasionally observed. A constant finding in patients with injuries of the spinal cord was great loss of weight, which usually was not regained, the mean of terminal loss of weight being 31.5 pounds (14.3 Kg.).

Hunger and thirst were experienced, as well as a sensation of fulness after eating. Nausea was produced by various appropriate stimuli, as well as by retained feces and calculi. Hiccup was produced by the usual causes. The water intake was greatly increased, particularly with lesions of the cervical portion of the cord.

An analysis was made of the causes of death, and the pathological changes in various organs were listed in their order of frequency.

DISCUSSION

Dr. John Martin: The group of patients just discussed by the authors had the best of nursing care. One is prone to think that decubitus ulcer is an indication of improper nursing care, but I wonder whether this attitude is entirely fair. Sometimes pressure sores will develop within a few hours, in spite of the care lavished on the skin, attention to nutrition and avoidance of infection and other untoward situations. This is seen in the brunet and thick-skinned, as well as in the blond and thin-skinned person. It is seen at times in both the thin and the obese patient. Everyone is familiar with the distressing condition of the patient who has the additional burden of pressure sores and knows that it is much better to spend every effort to avoid the condition than to cure it. I wonder whether anything was discovered in this study which would throw light on why bedsores develop in patients who from the first day of injury have received every care directed toward the avoidance of the ulcers.

Dr. F. Hiller: This clinical report contains many interesting observations on the abnormal functioning of the spinal sympathetic innervation after high transverse lesions of the cord. One cannot form a clear opinion without having studied patients with such lesions, as Dr. Chor and his co-workers have done. If I may single out one of the interesting results, I should like to comment on the frequent malnutrition which the majority of these patients have shown shortly after injury and during the later course of their illness. Appetite and hunger are complex

physiological phenomena, as has been recognized since the analyses of Cannon and Carlson. Hunger, as produced by contractions of the stomach and mediated through afferent vagal impulses, is obviously present in all these patients. Appetite, as a mixed physiological and psychological condition, is present so far as olfactory and glossopharyngeal stimulation is concerned. Apparently, however, the appetite is not sustained, and the patients do not eat enough. The fact that the majority of these patients have shown an abnormally high blood sugar level in the glucose tolerance tests makes one wonder whether the high blood sugar after food intake may contribute to the absence of sustained appetite. If this is true, administration of insulin ought, conceivably, to improve the nutritional state.

DR. C. THOMPSON: I should like to comment on Dr. Martin's question. In a study of about 200 patients with spinal cord injuries, my colleagues and I found a rapid and consistent disturbance in the protein metabolism and a marked loss of nitrogen. We do not know that this is a cause of ulcer in paraplegic patients, but certainly the evidence would indicate that it is a factor. In our experience, the use of insulin in stimulation of appetite was not efficacious in getting these patients to eat. No change in their metabolism resulted, as the authors have clearly shown. The incidence of decubitus ulcer can be greatly reduced by use of a high protein diet in the early course of the injury. In our study of blood pressures, the cervical lesion was associated with a consistent hypotension, but with hypertension as well, under the influence of bladder or bowel stimuli. Studies of the vascular effects of this induced hypertension are now in progress. The present indications are that the venous pressure is increased, the circulation time slowed and the cardiac output diminished. The heart size remains the same.

DR. LEO KAPLAN: I wonder whether the increase in blood sugar can be explained by the patient's decreased activity. Certainly, the activity of the paraplegic patient is minimal. Could the increase in blood sugar be a factor in facilitating the breakdown of pressure areas?

DR. JOSEPH TARKINGTON, Hines, Ill.: If in dogs with hypertension produced experimentally by partial occlusion of the renal artery a transection of the thoracic portion of the cord fails to reduce the hypertension, why do not patients with spinal cord injuries, with their high incidence of renal disease, show a higher incidence of hypertension?

DR. W. R. KIRSCHBAUM: The task of stimulating the frequently poor food intake of a paraplegic patient is not an easy one and is unlikely to be lessened by injections of insulin. The hyperglycemic (diabetic) patient may be very hungry, and the hypoglycemic patient may not have hunger at all. There is no evidence that the reduction of any circulating nutritive material acts on the brain to produce the sensation of hunger. It may be that an independent disturbance in the autonomic regulatory mechanism accounts for the difference in the approach to food or in the food intake.

DR. W. F. WINDLE: Perhaps I can contribute a point to the discussion, although I hesitate to emphasize our work because of its preliminary nature. During the past two years, with my colleagues, Clemente and Chambers, I have been studying regeneration in the spinal cord of adult dogs and cats and have demonstrated that a certain amount of intraneuronal regeneration is possible after complete transection of the spinal cord. This occurs only after proper steps are taken to inhibit development of scar tissue and glial membranes and to stimulate growth of connective tissue cells of a low order of differentiation, such as reticular cells and macrophages. We have used highly purified pyrogenic bacterial extracts (notably a pure carbohydrate constituent derived from certain bacteria and designated as pyromen,® marketed by Baxter Laboratories of Morton Grove, Ill.) to promote the connective tissue changes that are favorable to intraspinal neuronal regeneration.

During the course of our studies, we have had occasion to observe decubitus ulcers in a few of our experimental animals and to compare the healing of these ulcers in animals receiving this drug with the healing in those serving as controls. For example, in our most recent series, of 66 spinal cats (34 receiving pyromen® and 32 serving as controls), decubitus ulcers developed in four experimental and four control animals. The ulcers of all animals receiving pyromen® healed readily. The ulcers of the control animals, not receiving pyromen,® spread and became gangrenous, and three of the animals died as the result of these extensive decubiti. We have also had occasion to observe the effect of use of pyromen® in human patients. One

young man, in particular, who had sustained a cervical fracture dislocation with incomplete quadriplegia had an extensive and deeply eroding decubitus ulcer. The ulcer began to heal when treatment with pyromen® was begun six weeks after his injury, which occurred on March 22, 1950. I saw this patient in Dr. Howard A. Rysk's clinic at the Rehabilitation Center in New York on December 6. The ulcer was then completely healed; the skin was soft and pliant and freely movable over the lower portion of the sacrum, and from examination of the scar one could scarcely believe that this patient had had an extensive, eroding decubitus ulcer. Incidentally, this patient has regained some use of all his muscles, has full bladder and bowel control and has been discharged from the Rehabilitation Center.

From the standpoint of their action in inhibiting scar tissue and in stimulating the macrophage system, I believe that the bacterial pyrogens deserve to be given a thorough clinical trial. Several research projects are already in progress.

DR. H. CHOR: All here are familiar with the fact that lesions of the hypothalamus may produce disturbances of water metabolism, glucose metabolism and fat metabolism. These symptoms result from a disturbance of the autonomic regulatory centers, which are located in this area of the brain. In this presentation, we have called attention to similar disturbances in metabolism which may result from lesions of the spinal cord, especially at the higher levels. From my experience as a teacher of neurology for more than 20 years, I know that these symptoms have not been included in the clinical picture of disturbances due to injuries of the spinal cord. Our investigations have shown that interruption of the autonomic nervous system or its connections through the spinal cord does give rise to such metabolic alterations, heretofore not recognized. Our studies have shown that disturbance in cardiovascular regulation may give rise to unusual changes in blood pressure, such as postural hypotension and spinal hypertension.

In answer to Dr. Tarkington, I may say that, although in the basal state of patients with lesions of the spinal cord the blood pressure may be within normal limits, or somewhat low, any requirement on the part of the body to make new adjustments in blood pressure, such as change in position, may result in marked deviation from the normal. Likewise, we have found that striking alterations in sugar metabolism may occur with lesions of the spinal cord, these changes being a result of disturbed neurogenic control. To my knowledge, this has not previously been recognized as a possible symptom resulting from lesions of the spinal cord.

In answer to Dr. Martin's comment regarding bedsores: The two factors which have been emphasized are, first, a trophic influence exerted by the nerve supply to tissues, and, second, trauma. It is well recognized that it is desirable to avoid injury to denervated tissue, but there must be other factors responsible for the abrupt and severe breakdown of tissues which are not entirely understood. We are all happy to hear again from Dr. Windle; such research projects as he describes are of much interest and eventually will lead to a better understanding of the intricate problems involving the trophic state of tissues. Further studies are obviously necessary if one is to have a clear understanding of the many disturbances of the bodily state resulting from lesions of the spinal cord.

The Sensory Pattern in Partial and Recovering Lesions of the Spinal Cord. DR. BENJAMIN BOSHES, DR. MEYER BROWN and DR. RICHARD L. CROUCH (Hines, Ill.).

Thirty-six patients with injuries of the cervical or high thoracic region of the spinal cord were chosen for this study.

The usual method of recovery was a segmental recession from the level of the lesion caudad. In some cases, a return of sensation appeared first in multiple locations over the affected area; in others it appeared first in the lower sacral segments. A high degree of correlation of both pattern and degree of return was found between modalities conducted in the same funiculus, i. e., pain and temperature or vibration and muscle sense; and a lower degree of correlation was found between modalities conducted in separate funiculi, i. e., pain and vibration sense. This is considered evidence for return of function on an anatomic, rather than a functional basis, as proposed by the theory of paleosensibility versus neosensibility of Brouwer. In some cases, there was a notable dissociation of modalities conducted in the same funiculus. These exceptions

may be explained on the basis of some uncrossed fibers or a wide dispersion of fibers in the funiculus.

Bladder, bowel and genital sensations did not show a significantly different correlation with any of the somatic sensory modalities. This is considered further evidence against Brouwer's theory. No conclusions could be drawn as to the location of fibers carrying these visceral functions.

Motor return, including sphincteric control, was less frequent than sensory return, and return of sphincteric control was much less frequent than return of other motor functions. Return of motor functions did not show a significant correlation with return of sensory function.

A majority of patients began to recover during the first three months after injury. The longest period for the first return of function was four years. The degree of recovery does not necessarily depend on the time of return. Some patients with early return had a fair degree of recovery only. Some of those with long-delayed return had good or excellent recovery.

DISCUSSION

DR. A. J. ARIEFF: With reference to the time of recovery from injury, I had occasion to observe one of the paraplegic patients at the Veterans Administration Hospital at Hines, Ill., over a period of a few years. He was considered to have a physiologically complete lesion at the sixth cervical segment. About six years after his injury he complained of pain in the lower part of the abdomen and would point to the area which hurt. There was no local tenderness, and the area was, of course, anesthetic. Roentgen examination finally disclosed a gastric ulcer, which did not respond to management. I recently reexamined him because he was to have a laparotomy for possible gastric surgery (this being approximately eight years after injury); I then found that his upper abdominal reflexes had returned, indicating that his lesion was not complete. He may still show some recovery.

Electrodiagnostic and Electromyograhic Studies in Cases of Injuries to the Spinal Cord and Cauda Equina. DR. ALEX J. ARIEFF and DR. JOHN R. MULLINS (Hines, Ill.).

Spinal Cord Injuries.—Eighty muscles were examined in 32 patients.

In patients with injuries of the spinal cord (none below the sixth thoracic segment) the muscles, in spite of atrophy, showed no or few isolated electrical changes compatible with denervated muscles, even over many years. However, when areflexia without spasm was present (in 2 patients) the muscles showed the electrical changes, including electromyographic evidence, of denervated muscle. There was no correlation with the time after injury.

Lesions of the Cauda Equina.—One hundred and two muscles were examined in 31 patients.

Of the patients with physiologically complete lesions of the cauda equina, 66 per cent showed the picture of denervated muscle. In 33 per cent there were isolated electrical signs indicating an incomplete lesion.

In 90 per cent of the patients with physiologically incomplete lesions there were electrical signs of incompleteness or regeneration.

As time progressed, the severity of the atrophy increased and the rheobase increased, so that after three years the latter was usually over 25 milliamperes.

PHILADELPHIA NEUROLOGICAL SOCIETY

Helena E. Riggs, M.D., *Presiding*

Regular Meeting, Oct. 6, 1950

Dyspituitarism in a Dog: Clinicopathologic Study with Cinematographic Illustrations. DR. JOHN MCGRATH (by invitation).

The dog, a 3 year old pedigreed male beagle, was presented to the clinic of the University of Pennsylvania School of Veterinary Medicine because of alopecia, gradual increase in body size and progressive listlessness.

Physical examination showed a fat, lethargic dog, which weighed 39 pounds (17.7 Kg.). The animal appeared generally obese. The skin was thick and tense, and the coat of hair coarse

and dry with focal areas of alopecia. The genitals appeared small for an animal of his age. Blood studies, an electrocardiogram and roentgenograms of the head gave no pertinent information.

In the following year the dog showed, as dominant symptoms, chronic constipation, increasing obesity (the animal gained 21 pounds [9.5 Kg.], to weigh 60 pounds [27.2 Kg.] at death), hyperphagia, hypersomnia and diabetes insipidus.

The animal was killed and autopsied within three hours. Gross examination showed adiposity, involving the visceral organs as well as the subcutaneous tissue. Microscopically, the testes showed degeneration of many seminiferous tubules with decreased spermatogenesis. Histologically the thyroid gland suggested that of a hypophysectomized animal. Serial secretions of the pituitary gland, infundibular stalk and hypothalamus revealed a microscopic craniopharyngioma. The growth occupied the entirety of the cross sections of the infundibular stalk in its most anterior aspect. It was believed that some hypothalamic nuclei showed loss and degeneration of cells.

DISCUSSION

DR. H. M. MARTIN (by invitation): This case has been well discussed by Dr. McGrath. During my tenure of more than 30 years in the department of animal pathology, this is the first craniopharyngioma recorded in our series of tumors.

In veterinary medicine cases of spontaneous endocrinal disturbance are not often recognized clinically, the reason being that in many instances the symptoms are not noticed by the owner and therefore the animal is not brought to the attention of the veterinarian.

Most of our data on endocrine disease have been obtained from postmortem and histopathological studies. In the adrenal gland, most of our experience has been with neoplasms. Cortical adenoma is a common finding in old dogs. Clinical manifestations, if any, are not usually observed. We have in our collection a large adenoma of the adrenal cortex of a horse. This we associated with a hypertensive encephalopathy and with the clinical symptoms of a nervous nature (convulsions, etc.). Malignant tumors are not rare in the adrenal gland. We have studied a number of hypernephromas, or adenocarcinomas of the adrenal, with extensive metastases and associated secondary changes in dogs, horses and cattle. Degenerative conditions of the adrenal do not appear to be common. We had one case of such a state in a dog, in which the clinical syndrome and histopathological picture were suggestive of Addison's disease. Tumors of the testis are common in domestic animals, especially the dog. Clinically, enlargement of the organ seems to be the only change. The forms encountered have been seminoma, Leydig cell tumor, teratoma and carcinoma. Ovarian tumors in domestic animals are not uncommon. An interesting case observed was that of an arrhenoblastoma in a cow. Clinically the animal showed many masculine characteristics. Neoplasms, both primary and secondary, are frequently observed in the thyroid. A case of thymoma was also observed in a dog. We have noted a few cases of gastric disturbance in dogs which we believe may have been associated with hypothalamic lesions, similar to the syndrome suggested by Cushing.

DR. N. W. WINKELMAN: Some years ago, when Dr. Fox was in charge of pathology of the animals in the zoo, he asked that I examine all brain tumors in the animals autopsied. That sounded like a large project. In my work with Dr. Fox, in the course of some 10 years, he was able to send me not more than half a dozen such tumors. That is remarkable when one considers the number of clinics for the treatment of brain tumors in man.

I was wondering, therefore, what Dr. Martin's experience has been at the veterinary school. How many brain tumors has he seen in his 30 years' experience in animal pathology at the University of Pennsylvania School of Veterinary Medicine?

DR. CHARLES RUPP: Has Dr. McGrath any information on possible personality changes in the dog? Evaluation of an animal's personality is more difficult than that of a human being; but there has been some interesting work on personality changes in relation to the hypothalamus.

DR. H. M. MARTIN: In answer to Dr. Winkelman's question about brain tumors in animals, we have noted a number. During the past few years we have been examining more brains at autopsy, and therefore have found a higher percentage of tumors than in previous years. We have noted meningiomas, gliomas and many secondary growths, some of which we plan to report in the near future.

DR. JOHN T. MCGRATH: In answer to Dr. Rupp's question, the animal maintained a good disposition throughout life, with no personality changes noticeable.

Penetration of Fluorescein into the Spinal Fluid in Cases of Polyneuritis. DR. MARK GRIFFIN (by invitation) and DR. GEORGE D. GAMMON.

Nine cases of polyneuritis of diverse origin were studied for the penetration of fluorescein into the cerebrospinal fluid after an intravenous injection. In the cases in which the protein of the cerebrospinal fluid rose above 100 mg. per 100 cc. the fluorescein concentration rose in a manner roughly proportional. From this it is concluded that a part of the cerebrospinal fluid protein is derived from the serum, probably as a result of increased permeability of vascular and meningeal surfaces incident to the inflammatory change. Certain secondary effects which might result were discussed.

DISCUSSION

DR. GEORGE GAMMON: Of interest in this problem are the possible results of pressure paralysis due to the influx of protein into the interstitial spaces and nerves. We are primarily interested not in the fact that fluorescein gets from the blood into the spinal fluid but in the observation that its concentration rises along with that of protein and is therefore an indication of the functional character of the pathological lesion. I should like to have our neuropathologists, Drs. Riggs, Winkelman and others, comment on this thesis.

DR. N. W. WINKELMAN: This problem is by no means simple and easily solved. It is of interest that there should be an increase in fluorescein and protein in the spinal fluid in polyneuritis and not uniformly in other conditions, such as complete spinal compression, in which the protein level of the fluid is high. One of the possibilities may be a change in the permeability of the pial vessels in relation to the spinal roots. The fluorescein may well emerge with the protein in this condition.

This avenue of investigation in other, related conditions should be rewarding.

DR. HENRY A. SHENKIN: As I understand it, Dr. Gammon proposes the thesis that an increase in the permeability of the blood-brain barrier, with consequent increase in tension on the nerve fibers, may be responsible for the progression often noted in cases of polyneuritis. I believe, however, that an increase in permeability of the blood-brain barrier has previously been demonstrated in acute infections of the central nervous system, such as meningitis, with but rarely a progressive neuritis occurring as a complication. Penicillin has been shown to cross the normal blood-brain barrier very poorly, but in acute inflammations of the meninges the permeability of this barrier is apparently increased and penicillin enters the spinal fluid relatively freely. I wonder whether these facts can be reconciled with the thesis as proposed.

DR. HELENA RIGGS: The implication that in infections, virus or otherwise, there is an altered capillary permeability is very interesting. In my opinion, increase in protein is only an outward and visible sign of the changes in the partition of fluid between the intravascular and the extravascular compartment. Such a change would help to explain conditions like the Guillain-Barré syndrome, in which the pathologist sees very little inflammatory reaction to explain the symptoms.

With altered capillary permeability and tissue changes secondary to the shift in fluid, a disturbance in function could be present. Such implications are important in explaining the pathological process in certain conditions in which there is no inflammatory reaction.

DR. MARK GRIFFIN: In answer to Dr. Winkelman's question about the cases of compression of the spinal canal: We studied several cases of tumor of the spinal cord, in one of which there was complete block of the spinal cord with a protein content of about 1,000 mg. per 100 cc. In that condition, of a complete block and a protein level of 1,000 mg., not nearly as much fluorescein was appearing in the spinal fluid as in cases of polyneuritis with a protein level somewhat lower than 1,000 mg.

I should like Dr. Gammon to answer Dr. Shenkin's question.

DR. GEORGE GAMMON: What I am trying to ask is, Does the protein which has leaked into the cerebrospinal fluid, obviously through excessive penetration of the barrier, come from around the nerve roots and represent an additional compression paralysis engrafted on the original damage? The answer to that question might bear therapeutic fruit.

NEW YORK NEUROLOGICAL SOCIETY AND THE NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Harold G. Wolff, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, Nov. 14, 1950

Presidential Address: The Subject Matter of Neurology. DR. HAROLD G. WOLFF.

Patterns of Disorientation in Organic Disease of the Brain. DR. EDWIN A. WEINSTEIN and (by invitation) DR. ROBERT L. KAHN.

Patterns of disorientation for time and place were studied in 58 cases of tumor and vascular disease of the brain with diffuse delta activity in the electroencephalogram. In the acute stages of disorientation patterns were multiple and mixed, but in the process of reorientation they became discrete and relatively fixed. An early pattern of disorientation for place is that of verbal identification, in which the patient names the false and true identifications in the same sentence. The second pattern is that of misnaming or mispronouncing the name of the hospital or giving the name of a smaller institution closer to the patient's home. In the third pattern the patient names the hospital correctly but displaces it closer to his home or locates it in a place where he has been previously. In duplication, the patient gives the hospital in a false location but claims he has previously been in a similarly named hospital at the correct location. In the pattern of spatial condensation the patient names and locates the hospital properly but grossly underestimates the distance to his home. The pattern of the confabulated journey is usually the first manifestation of developing disorientation and the last in the recovery of orientation. It is not sufficient simply to ask the patient where he is to ascertain whether he is oriented for place.

In disorientation for date the patient generally gives a time antedating his illness, and in disorientation for time of day he judges the time in terms of his own sleep-waking activity cycle. On awakening from a nap he may consider it morning; so in ascertaining temporal orientation it is necessary to question a patient at several periods during the day. It was shown that states of partial disorientation do not depend on defects in memory, retention, calculation or perception. The importance in influencing patterns of disorientation of the motivation to be well and leave the hospital was discussed. Disorientation is not a manifestation of confusion or a random phenomenon, but an orderly aspect of a reorganization of cerebral function.

DISCUSSION

DR. HAROLD G. WOLFF: Were you able to correlate the patient's method of dealing with the environment during his illness with that of dealing with it before he became ill?

DR. EDWIN A. WEINSTEIN: Yes, we were. We studied the patient's premorbid personality from data given by friends and relatives and found that in the development of disorientation there was a correlation. These patients have a great drive for self esteem. In illness they regard any defect as an imperfection and react with a great deal of shame, or they try to ignore it. Although pathologic changes in the brain were present in all the patients with disorientation whom I studied, the degree of disorientation was not always comparable to the degree of cerebral damage.

DR. MORRIS B. BENDER: Studies in motor or sensory patterns are not too difficult, for it is possible to set up frames of reference which may serve as a background for the particular activity tested. However, in studies of mental function it is not easy to find a frame of reference. A mass of information can be gathered, but the problem is to unravel the data or to put order in the confusion of facts. The patterns which Dr. Weinstein and Dr. Kahn ascertained are fairly consistent and have been observed by other investigators. It is more significant that these patterns have been present throughout their period of observation, particularly during the period when the disorientation lessened, i. e., when the patient improved. I should like to ask two questions: First, does Dr. Weinstein consider the patterns of disorientation basic? I think that they are fundamental.

DR. HAROLD G. WOLFF: What do you mean by basic?

DR. MORRIS B. BENDER: Basic to the organism, or inherent. The second question is this: Would a change in environment produce an alteration of the pattern? I should not expect a change, since I consider the pattern as fundamental.

DR. EDWIN A. WEINSTEIN: I shall try to answer the second question first. I mentioned that all these patients were observed in the hospital. We had no opportunity to observe them at home, for we do not send patients home so long as they have manifestations of disorientation. I do not know what the manifestations would be if the patient went home. What Dr. Bender means by basic, I imagine, are the intrinsic properties of the nervous system. It is hard to say what a change in environment might produce. One certainly is not observing the direct action of the nervous system in any of the phenomena we have described, and these cannot be directly correlated with the particular mechanisms of the nervous system itself. In a sense, our problem is one of language. We tell you what the patient tells us. The patient with a damaged brain operates on a different symbolic level. What serves as a locus of time or place in conventional symbols now has another meaning. For instance, we had a paranoid patient who suspected the nurses of poisoning her, and when she was asked where she was, she said, "At Mt. Cyanide Hospital." She was expressing here her feeling about the hospital. She had a new level of symbolization. The drive to be well and to keep the organism intact is present in all people. It is expressed differently in a person with an intact brain than in a patient with a damaged brain.

DR. MAX LEVIN: I should like to ask a question in regard to the ease with which disorientation develops in the various spheres. In patients in severe bromide delirium, who are disoriented in all three spheres, I have found, in watching them recover, that they sometimes become oriented for place and person long before they become oriented for time. On the contrary, when a patient enters a delirium, he is likely to lose his orientation for time before he becomes disoriented in the other spheres. In other words, the sphere of time seems to be the most vulnerable of the three spheres. I wonder whether this accords with the experience of the speakers. There is, I think, good reason that the sphere of time should be the most vulnerable. The grasp of time is a much more complex function than that of place and person, as one can see in the young child. Place and person are concrete and tangible, while time is abstract and intangible. To a child, "Jimmie" is always a particular person, and "my house" a particular place. But "tomorrow" is much harder to grasp; "tomorrow" may be Monday, but on another occasion it may be Sunday. Children can recognize and name places and persons in their second year, but it takes them much longer to grasp the various concepts of time. This difference in complexity explains why, in delirium, time is the first sphere to go and the last to return.

DR. EDWIN A. WEINSTEIN: One point in the paper is concerned with how one tests disorientation for place. It is not sufficient to ask only where the patient is. He may name the hospital correctly, but may displace it or condense the distance, or he may elicit duplication or a confabulated journey. Disorientation for time and that for place in most patients cleared up together. We have had about 15 patients in whom disorientation for time persisted after that for place cleared up, and five patients in whom disorientation for place endured longer.

DR. THOMAS K. DAVIS: Has Dr. Weinstein sufficiently clarified the intermingling of amnesic elements in disorientation? I should not have thought about it before I heard his paper, because one tends to think of disorientation as specific. After shock treatments there is amnesia; I have seen patients in whom it took only the form of forgetting topographical items—where certain things in their home might be located, where this or that closet was or where the door to the cellar was. Is the kind of amnesia involving topographical relations which one sees after shock therapy different from the topographical variety which Dr. Weinstein has spoken of as a segment of disorientation?

Effects of Administration of ACTH to Patients with Myasthenia Gravis. DR. CLARA TORDA (by invitation) and DR. HAROLD G. WOLFF.

The effect of the pituitary adrenocorticotropic hormone (ACTH) on 15 patients with myasthenia gravis is briefly reported. The patients were men and women, of ages ranging from 18 to 61, who had had myasthenia gravis from one to 17 years. The mildly ill patients

were able to work on a daily neostigmine bromide intake of 45 mg., and the most severly ill patient was bedridden on a daily neostigmine bromide intake of 450 mg. ACTH was given in amounts of 500 mg. (25 mg. every six hours) once, twice or three times. The severity of symptoms before administration of ACTH and the degree of remission achieved after administration of the drug were studied by (1) clinical observations, (2) electromyography and (3) biochemical studies, consisting of the determination of the ability of blood serum to support acetylcholine synthesis.

During the last two days of administration of ACTH, and for a few days thereafter, a gradually increased disability occurred. One of the patients with so-called bulbar manifestations died on the third day of administration of ACTH. The severity of these symptoms seemed to be reduced by the concurrent administration of from 3 to 5 Gm. of potassium chloride by mouth during the period of ACTH administration.

During administration of ACTH the electromyogram and the ability of blood serum to support acetylcholine synthesis gradually increased and approximated normal values on the fifth day of administration of the drug. In many instances they have remained within normal limits to date.

Eleven patients exhibited a significant partial remission beginning the first week after the last injection of ACTH. The remission consisted in increased well-being, increased work performance on a reduced neostigmine bromide intake and increase of sensitivity to neostigmine bromide. Remission occurred both in patients not receiving potassium chloride durning administration of ACTH and in patients receiving potassium chloride. The occurrence of remission was difficult to establish in three patients who were mildly ill with myasthenia gravis.

To date, a complete relapse to the degree of severity of symptoms existing before administration of ACTH has not occurred in any of the 14 patients. Two patients showed a partial relapse after severe infections, and one, after a severe psychological shock.

New series of ACTH administration (500 mg. per series) induced further remissions.

DISCUSSION

DR. HAROLD G. WOLFF: Dr. Torda, it would be of importance to have you tell us what proportion of the 15 patients could be said to have been unequivocally helped by this procedure, it being assumed that there are a number of reasons that the others might not have been.

DR. CLARA TORDA: After administration of ACTH, the ability of the nerve-muscle system to maintain the amplitude of the action potential during repetitive stimulation returned to normal in all patients. Furthermore, the ability of blood serum to support acetylcholine synthesis became normal. Tolerance for neostigmine bromide decreased in all instances, and relatively small amounts of neostigmine bromide induced curarization. Infectious diseases were better tolerated than before administration of ACTH. One patient died the third day of administration of ACTH; 10 patients exhibited a remission, and for 4 the results were inconclusive.

DR. HAROLD G. WOLFF: From the practical clinical point of view, 10 of 15 patients may be said to have been helped, and the results in the others were difficult to evaluate.

DR. GILBERT H. GLASER: My colleagues and I have had a limited, but interesting experience with ACTH therapy in neuromuscular syndromes at the Neurological Institute. We have been concerned about the appearance of increased asthenia during the course of ACTH administration, and I should like to ask Dr. Torda whether she has determined the ability of the blood serum to support acetylcholine synthesis during the administration of the drug. This ability seemed to be increased in these patients after use of the drug was discontinued, but I should like to know about the acetylcholine synthesis during the administration of the drug. A decrease would help to explain the appearance of greater asthenia. We had a patient with severe myasthenia gravis, necessitating his being in a respirator, who showed striking, but transitory, improvement during ACTH administration. This, we understand, is a unique observation; and I wonder whether there have been other observations of improvement during the course of administration of the drug. In patients with dermatomyositis, particularly those with a myasthenic component, there has been a pronounced increase of the myasthenia, particularly weakness of the extremities. In one case, although the dermatomyositis was helped in

general, the drug had to be discontinued because of the increased weakness which developed. We have also noted severe asthenia during administration of ACTH in patients with other muscular disorders, such as progressive muscular atrophy and amyotrophic lateral sclerosis. We have administered potassium to these patients and have not noticed any improvement in the muscular asthenia produced during the administration of the ACTH.

DR. CLARA TORDA: The ability of blood serum to support acetylcholine synthesis increased the first day and returned to normal by the fifth day of administration of ACTH. The state reported by the patient often does not reflect exactly the condition of neuromuscular function. ACTH modifies many processes; one of them is responsible for the remission in patients with myasthenia gravis; others are responsible for the asthenia which develops during ACTH administration. The clinical state of the patient is probably the resultant of the various processes.

DR. HAROLD G. WOLFF: When did the patient in the respirator mentioned by Dr. Glaser begin to improve?

DR. GILBERT H. GLASER: He improved amazingly on the second day and was out of the respirator on the sixth day. He died about six weeks afterward, with severe respiratory complications.

DR. HAROLD G. WOLFF: Did you give him additional ACTH?

DR. GILBERT H. GLASER: No.

DR. PETER G. DENKER: Do these patients know what they are getting? I think this factor might have a bearing because of the tremendous publicity given recently to cortisone, which might introduce a psychological factor in the results observed.

DR. CLARA TORDA: ACTH has been administered in our laboratory to patients with myasthenia gravis since 1944, several years before either ACTH or cortisone received its "tremendous publicity." The first five patients did not know the nature of the agent injected. Intramuscular administration of placebos failed to induce an improvement of the ability to maintain the amplitude of the action potential during repetitive stimulation and the ability to support acetylcholine synthesis.

DR. HAROLD G. WOLFF: That is the very point to be emphasized. It is for this reason that measurement of action potentials is used. The action potential is not dependent on motivation, since the ulnar nerve is stimulated directly. It does not involve a central integrative function.

DR. CHARLES KANE: I should like to make a few comments based on a limited personal experience with three myasthenic patients treated at the Veterans Administration Hospital, Kingsbridge Road, New York, first because the long-term results are somewhat different from those in Dr. Torda's series and, second, because my patients experienced, by being given large amounts of potassium, relatively little discomfort during the administration of the drug. Dr. Torda tested my patients and was most helpful throughout the period of the study.

Any clinical neurologist attempting to assay the value of ACTH in myasthenia gravis will ask himself one of three questions: 1. Is the new agent "specific," in the sense of being curative? I believe, on the basis of what we have heard tonight, together with my own experience and that of the Mayo Clinic, that we must conclude the drug is not a "specific" agent in the treatment of this disease. We do have definite evidence that it is capable of producing rather long-lasting, if partial, remissions. This is of considerable interest, because I believe we know the basic physiological process of the disease, which has been worked out by Dr. Torda and Dr. Wolff as a result of extensive investigations in the past seven years. It is thought by these investigators that the disease is due to a deficiency in acetylcholine synthesis, the precise mechanism of this being still unelucidated. 2. If ACTH is not a specific curative agent in myasthenia gravis, do the beneficial effects of the drug outweigh the disadvantages? Although there are less than 30 reported instances of the use in this drug in myasthenia gravis, it is fair to conclude that in proper hands the margin of safety is adequate. 3. Does the use of this agent add anything to the theoretical knowledge of the disease? I believe the answer, again, is in the affirmative.

At this point, it may be of interest to point out a fundamental concept, recently popularized by Dr. Walter B. Cannon, of Harvard Medical College (Cannon, Walter B.: The Way of an Investigator, New York, W. W. Norton & Company, 1945). According to this concept of serendipity, most progress in medicine and the natural sciences has occurred purely by chance. It would appear that in the use of ACTH for myasthenia gravis we have an instance which is rather unusual in medicine, one in which careful clinical research proceeding along definite lines suggested by important basic physiological experiments has resulted in a significant contribution to the knowledge of disease.

To become more practical my colleagues and I have treated three myasthenic patients with ACTH at the Kingsbridge Veterans Administration Hospital. All these patients were moderately or severely ill when admitted to the hospital. One patient was paraplegic, in addition to having myasthenia gravis. Each patient received the standard course of therapy with ACTH. With the administration of 15 Gm. of potassium daily, given in eggnog, all these patients tolerated the drug exceedingly well, with no significant side effects. Promptly after therapy the condition of all the patients improved. One patient experienced a total clinical remission lasting three and a half months. For the second patient the requirement of neostigmine following treatment was reduced significantly, but within a month the patient was taking essentially the same dose as before treatment. In the third patient, a paraplegic with severe myasthenia gravis, we were not impressed with the results of two courses of ACTH, given six weeks apart. However, it is important in each of these cases to stress that the laboratory tests outlined by Dr. Torda showed improvement after therapy.

Of the three patients we treated, only one is still alive. One patient died apparently of pulmonary edema and bronchopneumonia five months after treatment, and six weeks after a remission lasting three and a half months. Necropsy was not done. The second death was that of the paraplegic patient, and in this case necropsy was performed. We are awaiting the final pathological report. The third patient is being followed at monthly intervals in the clinic and is now taking the same amount of neostigmine as before treatment. His disease has not advanced in the past year.

I have the following questions to ask Dr. Torda: Of the patients in the New York Hospital series, how many are still alive? In how many patients was the disease static or progressing rapidly at the time that therapy was started? What is Dr. Torda's idea of the long-lasting effects of the therapy? The treatment is apparently not a substitution type, but one in which a basic process is stimulated.

Finally, I wonder if it might not be profitable to explore the results of the tests such as Dr. Torda has outlined in clinical conditions characterized by a striking asthenia (i. e., hyperthyroidism) or, let us say, during the clinical improvement which occurs in myasthenic women during the second and third months of pregnancy.

This is a fascinating new approach to the problem of myasthenia gravis. From my own limited experience with ACTH, I would conclude that such treatment should be restricted to research centers for two reasons: the expense of the drug ($50 for five days' treatment), and the hazards of the treatment. Furthermore, it is only by carrying out such careful objective tests as Dr. Torda has described that the true value of this agent can be assessed in a disease subject to unpredictable remissions and exacerbations.

DR. CLARA TORDA: One series of treatments, with a total dose of 500 mg., is not sufficient to induce more than a partial remission, of varying duration. Prolonged administration is not practicable, and repeated administrations of a series of a few hundred milligrams are probably required to achieve the optimal result.

In pregnancy it is assumed that the secretion of ACTH is increased. Furthermore, during pregnancy the concentration in the body of some steroid substances increases. A few of these steroids increase acetylcholine synthesis (Torda, C., and Wolff, H. G.: Effect of Steroid Substances on Synthesis of Acetylcholine, *Proc. Soc. Exper. Biol. & Med.* **57**:327, 1944. Torda, C.: Effect of Hormones on Concentration of Striated Muscle and on Cholinesterase Activity, *ibid.* **51**:121, 1943).

Epinephrine and ephedrine increase acetylcholine synthesis (Torda, C., and Wolff, H. G.: Effect of Epinephrine on the Synthesis of Acetylcholine, *Proc. Soc. Exper. Biol. & Med.* **56**:

86, 1944; Effect of Alkaloids on Acetylcholine Synthesis, *Arch. Biochem.* **10**:247, 1946), and it is assumed by some investigators that epinephrine increases the release of ACTH (Selye, H.: Factors Influencing the Corticotrophic Production of the Anterior Pituitary, *J. Clin. Endocrinol.* **8**:588, 1948).

The observation that patients with myasthenia gravis show impairment during hyperthyroidism parallels the result of animal experiments, namely, that administration of thyroxin and the thyrotropic hormone of the pituitary gland decreases the ability to maintain the amplitude of action potential during repetitive stimulation in both healthy and hypophysectomized animals (Torda, C., and Wolff, H. G.: Effect of Pituitary and Adrenocortical Hormones on Neuromuscular Function, *Am. J. Physiol.* **163**:755 [Dec.] 1950).

One of the 15 patients died the third day of administration of ACTH, and the 14 are alive and well. In 12 the disease was static, and in three it was progressing. The remission was long lasting in the sense that whenever relapse occurred it was partial.

Treatment of Psychomotor Syndromes by Operations on the Temporal Lobe. Dr. J. Lawrence Pool, Dr. William Langford and Dr. Gilbert H. Glaser.

Two cases of psychomotor epilepsy were described. Both patients had episodic attacks that were clinically similar in many respects. Both children were afflicted with some degree of emotional and mental retardation, thickness of speech, severe restlessness, abnormal behavior and unilateral electroencephalographic changes. In addition, the age and character of onset of the disease process were quite similar in the two patients. Psychotherapy and anticonvulsant medication had failed to help either patient to any appreciable extent prior to surgical intervention, so that both had to be confined to an institution, whereas since operation both patients have been restored to their homes.

Both patients have shown excellent improvement in behavior, attention span, electroencephalographic tracings and reduction of seizure incidence since unilateral anterior temporal lobotomy (case 1) or temporal lobectomy (case 2). Attention is directed to the fact that clinical benefit, as well as improvement in the electroencephalogram occurred in case 1, even though the operation was carried out at a distance from the principal focus of electroencephalographic abnormality.

These patients show the typical temporal lobe seizure complex, as described by Penfield and Flanigin (Arch. Neurol. & Psychiat. **64**:491 [Oct.] 1950), indicating that the psychomotor syndrome may be part of the picture of the temporal lobe seizure state.

Theoretical consideration regarding possible mechanisms of the favorable influence of anterior temporal lobe surgery were discussed, with particular reference to the role of the rhinencephalon and associated cortex.

DISCUSSION

Dr. H. Houston Merritt: We are indebted to Dr. Pool for calling the attention of this group to the temporal lobe. Interest in the temporal lobe has sprung up all over the country, and a great deal of work has been done in Chicago and Montreal, but, so far as I know, there has been little interest in the subject in New York.

Dr. Pool mentioned the importance of the temporal lobe in regard to the electrical activity of the entire cerebrum. It has been shown that the temporal lobe is important in the regulation of the electroencephalogram, particularly since abnormalities may spread rapidly to other parts of the brain. It is thought that impulses from the temporal lobe discharge into the thalamus, so that a small lesion in the temporal lobe may produce widespread disturbance in the activity of practically the whole cortex. In my opinion, we must reserve decision in regard to the role of the temporal lobe in convulsive seizures and abnormal states of consciousness. There is as yet insufficient evidence to conclude that temporal lobotomy or the removal of foci in the temporal lobe are a cure for psychomotor epilepsy or for abnormal behavior. There is enough indication in the work of Pool, Gibbs, Bailey, Penfield and others to lead us to feel that the subject should be studied thoroughly.

I should like to ask whether pathological examination was made in case 2 and, if so, what was found.

DR. J. LAWRENCE POOL: Studies were carried out by Dr. Abner Wolf on biopsy material from both patients, and no pathological changes were found in the cytoarchitecture of the cells or in the vascular pattern in either case.

DR. THOMAS K. DAVIS: I apologize for speaking twice on this program, but I should like to raise a question which I think ought to be in the record. The question is whether Dr. Pool has described true psychomotor attacks in his two patients. He has described episodes which I should not call psychomotor. On the other hand, in the first patient, the running attacks, in which the boy ran a mile and did not know where he was, may have been psychomotor, but these were not so labeled. I do not believe that the other child had psychomotor attacks. Probably Dr. Pool has material not incorporated in his paper which bears on this question more fully.

DR. H. HOUSTON MERRITT: In the second case, I would agree, the attacks as described could not be classified as of psychomotor, but those in the first case, with salivation, movements of the jaw and confusion, could be so classified. I wish Dr. Pool would read the description of these attacks.

DR. J. LAWRENCE POOL: In case 1 the attacks were characterized by an aura of vertigo and faintness and were generally initiated by staring ahead or smacking sounds, after which face and mouth movements would occur, accompanied with profuse salivation. Salivation and thickness of speech were often noted for 10 minutes after an attack, while vomiting frequently occurred immediately after a seizure. Occasionally, but not always, the boy lost consciousness, and usually the body seemed limp or relaxed during a spell. That *alone* I should not necessarily consider a psychomotor attack.

DR. H. HOUSTON MERRITT: I should. That is what I should call a psychomotor attack.

DR. J. LAWRENCE POOL: More characteristic of psychomotor epilepsy seemed the fact that in some attacks the patient would walk with one hand out in front of him, as though holding a candle, and the other hand at his side, while being unresponsive to questions. In addition, he was subject to periodic running attacks of which he was not aware.

We wish to stress that the electroencephalogram of neither of these patients was typical of the Gibbs syndrome. Both patients got better despite the fact that in neither case was a direct surgical attack made on the electroencephalographic foci.

The point I meant to make, and stated in the paper, was that these attacks were psychomotor states apparently closely resembling many of those reported by Penfield, who refers to the "psychomotor state" and thus avoids the term "psychomotor epilepsy." The psychomotor state includes the abnormal behavior of different types, so that it is perhaps a better term.

DR. JOSEPH G. CHUSID: It might be well to remember that the Gibbses and Fuster (Gibbs, E. L.; Gibbs, F. A., and Fuster, B.: Psychomotor Epilepsy, ARCH. NEUROL. & PSYCHIAT. **60**:331-339 [Oct.] 1948) demonstrated that the essential thing in so-called psychomotor epilepsy in the cases selected for operation is the presence in the electroencephalogram of a prominent spike focus in the temporal lobe. In the original group operated on by Percival Bailey, the spike focus was present in the anterior part of the temporal lobe, or temporal tip, of one or both cerebral hemispheres and had the property of becoming greatly accentuated in sleep, either natural or drug induced. The routine used in many cases in which such a state was suspected and in which the waking electroencephalogram was not remarkable was to give the patient a barbiturate or other anesthetic; under such conditions these spike foci frequently became apparent. At St. Vincent's Hospital we have had experience with two patients. The first, a man of 32, had nocturnal seizures and severe personality and behavioral changes. In a routine electroencephalographic test, a spike focus was detected in one temporal tip, and in light sleep such a focus was found in both temporal tips. The electrically most abnormal side, which was the nondominant side, was operated on first, approximately 2½ years ago, and the temporal tip was excised by suction. The patient's subsequent clinical course was relatively unchanged; he had seizures frequently and presented a difficult personality problem. He was studied again and in an electroencephalographic recording during sleep a spike focus was found in the temporal tip of the opposite side, and the second temporal tip was subsequently excised. Thereafter his seizures continued almost unchanged; however, he has been somewhat less aggressive and more agreeable, albeit not cured.

The second patient, a youth of about 17, was seen initially because he presented a severe behavior and personality problem with frequent generalized seizures. He was studied in the routine manner, and he, too, showed a pronounced spike focus in the anterior portion of the right temporal lobe during light sleep; the tip of the right temporal lobe was surgically removed. The sleep electroencephalogram made about a month after operation did not disclose a spike focus in the temporal lobe, and at that time the mother felt that his condition had improved, since the seizures were less frequent. Further follow-up study has not been possible.

DR. LEWIS J. DOSHAY: I believe the question was raised whether the seizures in Dr. Pool's second case were psychomotor. This boy had grand mal seizures when he was 3 years of age. They changed to petit mal during the succeeding 11 years, during which time he had 20 to 40 such attacks a day, interspersed with an occasional grand mal seizure. During the past three years the petit mal seizures had disappeared and for them were substituted nocturnal psychomotor spells; the latter occurred once a night or once in two or three nights, interspersed with grand mal seizures once in three to six months. The psychomotor attacks occurred not only during the night, but also by day if he took a nap. These seizures were ushered in by a scream, after which he would sit up in bed, his eyes would be glazed and his face flushed. He would pass through chewing motions with his jaws, smack his lips, work his mouth and make peculiar swallowing sounds repeatedly. Occasionally there would be a slight flow of saliva from the mouth. He would move about in bed in an aimless automatic fashion, either pulling the blankets toward him or pushing them away, or lifting the pillow and working his hands around as though looking for something. On a few occasions the spell was ushered in by several jerky movements of the right arm and leg, and at such times he would rub the right side of his face and his right arm with his left arm. During other spells he would get out of bed and walk about the room aimlessly for several minutes, touching various objects, and then return to bed. The family never knew what he was looking for, because he had complete amnesia for the spells. Toward the end of a seizure his face would show pallor, rather than flushing. The attacks would last from one-half to three minutes.

These spells cannot be considered petit mal, of which he used to have 20 or more seizures a day and which he left behind him three years ago; nor could they by any stretch of the imagination be considered grand mal seizures. The automatic movements of rubbing his hand and face, of searching for things in bed, of walking about the room, of chewing, swallowing and smacking movements of the lips and the occasional sialorrhea clearly denote a classic syndrome of the mild variety of psychomotor attacks, as delineated by William G. Lennox (Childhood Epilepsy, *New York State J. Med.* **50**:2263 [Oct. 1] 1950). According to Dr. Lennox, petit mal seizures are limited to a triad: (1) a black-out of consciousness, lasting but a few seconds; (2) myoclonic jerks of the arms, and (3) astatic, or drop seizures, which result in head nodding or in sudden flaccid collapse of the body. Psychomotor seizures are, on the other hand, of various sorts: (1) brief periods of increased muscle tonicity, with chewing, aimless motions, smacking the lips; (2) attacks of violent rage or running fits, and (3) automatic activity with ambulatory automatisms. With the passing of years petit mal seizures tend to die out, whereas psychomotor seizures begin to increase, probably because of damage to the temporal lobes from repeated convulsions or trauma. One cannot fail to notice that in Dr. Pool's case the seizures were not of a few seconds' duration, as in petit mal, but lasted half a minute to three minutes and were accompanied with all the classic symptoms of psychomotor seizures enumerated by Dr. Lennox—chewing, smacking of the lips, swallowing, aimless and random movements and ambulatory automatism. Therefore, there can be no question that the boy's seizures were of true psychomotor type. This position is further supported by Dr. Merritt's observations (Recent Advances in the Treatment of Epilepsy, *New York State J. Med.* **46**:2630 [Dec. 1] 1946). He emphasized that the psychic equivalent, or psychomotor attacks, is a term used to describe a heterogeneous group of epileptiform disturbances which do not conform to the classic grand mal or petit mal type of seizure. The milder psychomotor attacks are often confused with petit mal attacks, but they differ from the latter in that the duration of the period of mental cloudiness is greater and the range of muscular

movements is much more widespread. Petit mal attacks last for only a few seconds, during which there is a transient clouding of consciousness. Psychomotor seizures, on the other hand, differ from grand mal attacks in that the patient does not fall to the ground in a tonic-clonic seizure with complete loss of consciousness.

DR. WILLIAM S. LANGFORD: As one who observed Dr. Pool's first patient, I should like to add a little information. The child was first seen in 1938 at 3 years of age, when he presented hyperactive and repetitive behavior. Phenomenologically, he displayed the signs and symptoms that we have learned to associate with the schizophrenic-like psychoses in children. Speech onset was delayed and for some time was replete with echolalia and pronomial confusions. It was not until he was 7 years of age that he could carry on any sort of a conversation. At that time, too, he first began to play with toys in the usual manner. Up to then his activity had been limited to spinning things or throwing them. He clung to adults and resisted any relationship with children, in the way in which these children do. The diagnostic picture, however, has never been clear: He has always presented many features which suggest a diffuse encephalopathy as a cause of his behavior. His attacks did not come on until about the age of 11½. The onset was with lip smacking, twitching of the mouth and pronounced salivation. In the two of the attacks I observed some automatic activity. Since operation he has been quicker and less distractable; the impulsiveness and unpredictability have cleared. He has rather rigid self control. He is now in the regular eighth grade of the school, which he attends, and is out of the special class. He is working hard in school and is accepted by the other children. Two other things have happened since operation: On the Rorschach test, the color naming, present preoperatively, has disappeared, although he still sees certain things as leaves because they have hands and feet. Another symptom which has cleared since operation has been the rotation around the longitudinal body axis on turning of the head, described by Bender as characteristic of, but not limited to, juvenile schizophrenic patients. The relationship of the long-time personality disturbance to the psychomotor attacks is not clear, but the postoperative changes in behavior are well defined.

Book Reviews

Sex Questions and Answers: A Guide to Happy Marriage. First Edition. By Fred Brown, Ph.D., and Rudolf T. Kempton, Ph.D. Pp. 256, with 4 figures. Price, $2.95. Whittlesey House Division, McGraw-Hill Book Company, Inc., 330 West 42d St., New York 18, 1950.

This book contains the answers to 1,126 questions on sex, which have been classified and divided into 13 groups or chapters. The questions, the authors feel, are of definite interest to the layman, since they are the actual questions submitted anonymously to the authors by men and women of the United States Army when both authors were teaching at the Army's American University in Shrivenham, England, in 1945.

The first chapter, "The Biology of Sex," contains three of the four figures, all of which are schematic line drawings pertaining to the structure of the male and female organs. The fourth figure, appearing later, is one showing full term pregnancy. The remaining 12 chapters contain questions which touch on the very subjects which patients daily ask their physician, psychiatrist, psychoanalyst or psychologist.

The questions are answered directly, in an easy-to-read manner, understandable to the layman. Many questions call for opinions and statistics—e. g., "What is the effectiveness of the various contraceptive methods?" "What is the percentage of women who experience orgasm in marriage?" "Is the 'genital kiss' abnormal?" For answers to questions calling for opinions, the authors rely heavily on such authorities as Havelock Ellis, Kinsey, G. V. Hamilton and A. A. Brill.

The physiological aspect of the answers were taken up by Dr. Kempton, chairman, Department of Zoology, Vassar College; the psychological aspect by Dr. Brown, clinical psychologist, the Mount Sinai Hospital; adjunct associate, professor of psychology, New York University. One statement, however, "It is very rare for a person to have neurotic symptoms if he enjoys a satisfactory sex life because the latter is not possible unless he has achieved an adequate level of personality development," needs further explanation. The author fails to include the psychosexual fixations of infancy and childhood as an explanation of the etiology of the neuroses in adults who do enjoy a satisfactory sex life (at least satisfactory to themselves). The author's statement, coming at the end of a chapter dealing with adult sexuality, leaves one with the feeling that infantile sexuality plays no part in the production of the neuroses.

The Psychoanalytic Study of the Child. Volume V. Edited by Ruth Eissler, Ann Freud and Edward Glover. Price, $7.50. Pp. 416. International Universities Press, Inc., 227 West 13th St., New York 11, 1950.

This fifth volume of the annual study in child analysis continues the editorial tradition of reporting in original papers on the progress of recent advances in child analysis. The first six papers constitute outstanding studies dealing with the relation between psychoanalysis and developmental psychology. Known to the worker in the field is Rene Spitz's report on his "direct infant observations" and their relevance to ego psychology. Edith Jacobson's paper on the wish for a child in boys is not only of interest in the normal psychology of the infant boy, but also of great significance to the analyst working with grown-up men. The quality of all the contributions is high, and there is hardly a worker in the field of child psychiatry and child analysis who will not find stimulating reading. The last papers in the book, by Rangell and Bonnard, give unusual aspects of child therapy.

Pedigrees of Negro Families. By R. R. Gates. Price, $5.50. Pp. 267, with illustrations. The Blakiston Company, 1012 Walnut St., Philadelphia 5, 1949.

Pedigrees of Negro families are apparently about the same as for those of any other racial group. Only one disease, sicklemia, seems to be characteristic of Negroes. The normal traits discussed are also much the same as those for white folks except that musical ability appears

to be commoner and more remarkable among Negroes. This is well discussed in chapter 7, and several convincing family trees are given as evidence. Left handedness and ambidexterity are considered and charts are shown, but no conclusion is drawn as to what the type of inheritance may be. The author's statement, "It is known that in right handed persons the sulcus lunatus . . . is on the left side" would not be accepted by many. Nor would his statement that "stuttering probably arises only when a change from left to right as the functionally active hand is forced on the child too early" be acceptable to persons conversant with the field of speech therapy.

Chapter 8, on "Abnormal Nervous and Mental Conditions," contains a great many data of interest to neurologists and psychiatrists. Some subjects, such as enuresis, seem to be dragged in without adequate evidence of genetic cause. The family tree of this disorder (fig. 168) shows two cases in four generations, with 39 representatives—good evidence against inheritance, one might surmise. Interesting data are given on "feeblemindedness," but the term is used too loosely to indicate always just what condition is referred to. The same can be said of charts showing "insanity" in families. This term used "in the general sense" is meaningless, the cases referred to being probably schizophrenia. Some impressive facts are given concerning the inheritance of schizophrenia. Chart 182 shows the 56 descendants in four generations of a pair of "schizoid psychopaths"; 29 are affected.

"Manic-depressive insanity" is introduced with the sentence: "This is universally recognized as a distinct form of psychosis from schizophrenia; yet a manic-depressive quite frequently has a schizophrenic child." One wonders what authorities Gates uses. Certainly, many psychiatrists believe that manic-depressive and schizophrenic psychoses are closely related and often so overlapping as to be called "schizo-affective" and considered indistinguishable. Gates cites a collection of 10 families in which "an affective and a schizophrenic morbid predisposition have come together in the parents," with the result, among 60 descendants, of 6 with pure manic-depressive psychosis, 4 with pure dementia precox and 10 with commingled features of both. Nevertheless, he believes that, "in contrast with schizophrenia, the evidence indicates that manic-depressive psychosis is determined mainly by a dominant gene."

The book is readable, profusely illustrated and full of interesting observations. These include not only the disease mentioned above, but many medical conditions and many normal characteristics, such as color, size and hair.

Psychotherapy. By Paul Schilder, M.D. Revised and enlarged edition, arranged by Lauretta Bender, M.D. Price, $5. Pp. 409. W. W. Norton & Company, 101 5th Ave., New York 3, 1951.

In the preface to the first edition, published in 1938, Paul Schilder states: "It has often been said that for a psychological approach to the patient the physician needs but two mysterious qualities: a personality and intuition. But these two qualities, without knowledge and training, would hardly suffice for surgery. Neither do they for psychotherapy." To supply this knowledge and training, this book was written, and it has found its place in medical teaching. It often reads like the protocol of lectures to students in a psychotherapy seminar. It has the advantage and the disadvantage of such an informal approach. Paul Schilder's work was one of the first attempts to criticize, evaluate and synchronize psychotherapy in its various aspects, and as such it will be welcome. Lauretta Bender has revised and enlarged the new edition. Of special use is the bibliography, which is brought up to date.

Neurology and Psychiatry in General Practice. By Henry R. Viets, M.D., in collaboration with C. Charles Burlingame, M.D.; Clarence B. Farrar, M.D., and Z. M. Lebensohn, M.D. Price, $3.05. Pp. 150. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1950.

At the Clinical Session of the American Medical Association in December 1949, a three day program was devoted to neurology and psychiatry. These discussions have been used as a basis for this book, which is to be considered not as a complete treatise, but, rather, as a summary. Enough has been set forth to give the general practitioner a helpful insight into the present state of knowledge of some diseases of the nervous system and their treatment. The neurological topics range from epilepsy to parkinsonism, the rehabilitation of the disabled

neurological patient and the evaluation of the electroencephalogram. The psychiatric part is so cautious and conservative, avoiding all controversies of present day psychotherapy and psychodynamics, that it will hardly hold the interest of the general practitioner.

Fainting, Physiological and Psychological Considerations. By George L. Engel, M.D. Price, $2.75. Pp. 153. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

This monograph represents an attempt to understand the mechanisms and clinical characteristics of the various types of fainting in the light of present knowledge. While the author hopes to provide a sound scientific basis for the understanding of syncope, it is his goal to present the subject in a form that will be useful to the practicing physician, who is faced with the practical problems of diagnosis and treatment. The psychosomatic aspects of fainting are mentioned, but strangely neglected.

The Abnormal Pneumoencephalogram. By Leo M. Davidoff, M.D., and Bernard S. Epstein, M.D. Price, $15. Pp. 506, with 659 illustrations, in 289 figures. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1950.

This is the long-awaited companion volume to the classic work of Davidoff and Dyke on the normal encephalogram, published in a second edition in 1946. This second volume was much more difficult to write because of the enormous number of abnormalities that had to be sifted, classified and explained on the basis of postmortem examination. Fortunately, the technics for taking the roentgenograms have been perfected over the years, so that brilliant pictures are obtained. It is a pleasure to see so many true lateral and true frontal films, which make comparisons the easier. In some cases the size of the reproductions is a bit small for adequate demonstration of the pathological changes, but this is compensated for by indicative arrows.

The text is clear, condensed and appropriate, but the illustrations and the accompanying legends are the real meat of the book. It is interesting to compare the amount of space devoted to certain subjects, such as tumors or hematomas, as compared with that given to similar subjects in books on clinical neurology or neuropathology. For instance, in the case of multiple sclerosis, there is always abundant material in other textbooks, but here the presentation of the subject, while based on 10 cases, is not as full in the description of the variations of the disease as might be anticipated. Presumably, the roentgenograms available on multiple sclerosis came from rather early and atypical cases, in which differential diagnosis was important. There are no illustrations from far advanced cases of the disease. Nor are the huge ventricular dilatations and cortical air shadows frequently seen in the late stages of Pick's and Alzheimer's diseases sufficiently stressed. On the other hand, the pneumoencephalographic appearances of the congenital anomalies are particularly well presented.

The discussion of intracranial tumors occupies well over half this fine volume. Nowhere else can such an intensive study be found, correlated with the anatomic appearance in a large number of instances. Case histories from the authors' experience are freely used, and in each chapter there is a general discussion of the pertinent literature.

The pneumoencephalogram has become such an important diagnostic aid in the study of intracranial disease that this authoritative work will occupy a place of honor in any service devoted to neurology, neurosurgery and neuroradiology. The authors and the publishers are to be congratulated on bringing out a fine volume.

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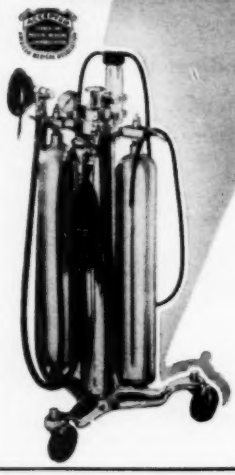

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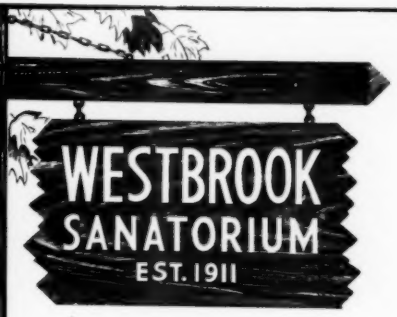

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